ANNALS OF
INTERNAL MEDICINE

MAURICE C. PINCOFFS

Editor

VOLUME 19

(OLD SERIES, VOLUME XXIV)

July to December, 1943

Contents

NUMBER 1, JULY, 1943

NUMBER 2, AUGUST, 1943

NUMBER 3, SEPTEMBER, 1943

NUMBER 4, OCTOBER, 1943

NUMBER 5, NOVEMBER, 1943

NUMBER 6, DECEMBER, 1943

EXPERIENCES ASSOCIATED WITH A TRANSFUSION UNIT IN A 700 BED HOSPITAL: AN ANNUAL SURVEY OF OVER 3,500 ADMINISTRATIONS OF BLOOD AND PLASMA (DRIED) *

By LOWELL A. ERF, M.D., and HAROLD W. JONES, M.D., F.A.C.P.,
Philadelphia, Pennsylvania

THE purpose of this analysis is to discuss some of the clinical experiences and the practical problems associated with the Blood Transfusion-Plasma Unit † of Jefferson Hospital for the year ending July 1, 1942.

TECHNIC

a. Preparation of Blood and Equipment Used. During the year no bottle of blood was used for a transfusion after four days of storage. Many of the qualities of blood change after that period of storage.[1,2] Since there were relatively few colored donors, colored blood was given to colored patients or used for plasma.[3] Blood was typed and crossmatched by the Landsteiner technic. The apparatus for collecting and dispensing blood (including cellulose tubing) was purchased from Hospital Liquids Incorporated; both the 750 c.c. vacuum bottles and the 650 c.c. centrifuge vacuum bottles were used. Because rubber tubing is becoming scarce and because the danger of pyrogens is probably minimized in cellulose tubing, which is discarded after the initial use, cellulose tubing was used for the administration of blood and has proved to be a very satisfactory substitute. All of the blood transfused was citrated and was administered cold as it came from the ice box, the temperature of which was maintained at 35° F.

A card attached to each bottle of blood taken from the bank had the name of the donor, the date the blood was withdrawn, the type of blood contained, the results of the serologic tests (both Kahn and Wassermann), the name of

the recipient and the name of the technician who performed the crossmatching. After each transfusion the attending nurse must sign the card attached to the bottle indicating that the patient did or did not have a reaction following the transfusion. Of 2,869 transfusions during the year, in only three instances was blood administered other than the type identical to that of the patient's (3 bottles of citrated blood of type "O" were given to three patients with type "A" blood) and of the three, one patient suffered a hemolytic reaction (see case reports). We feel that homologous blood should be administered but there is good evidence that blood from universal donors is usually safe. Rosenthal and Vogel[4a] have shown that in over 800 transfusions of universal donor blood no more reactions occurred than when homologous bank blood, or when the old indirect transfusions of homologous blood were used.

Aubert et al.[5] demonstrated that in 40 per cent of donors of group "O," anti-A titers of over $1:512$ were found and noted that transfusions of "O" blood of such high anti-A titer, or higher, rarely produced an elevation of the red blood cell levels of recipients of group "A." Neither did they produce severe or fatal hemolytic reactions. They concluded that when a transfusion is designed to raise a recipient's red cell count homologous group blood should be given, but in emergencies when restoration of blood volume is required universal donor blood is justified.

The technic followed for cleaning needles and rubber tubing was described by Lewisohn and Rosenthal.[6, 1] The scrupulous cleanliness of these articles was found to be of the utmost importance in preventing post-transfusional febrile reactions.

b. Plasma. The outdated blood, that after four days of storage, was either separated (DeLaval separator) or centrifuged, the plasma withdrawn (either by the open or closed systems), then pooled to reduce agglutinin titer, frozen in glass containers, dried by the Hill Adtevac machine [7] (a most practical machine since the hydroscopic agent, silica gel, can be used over and over again) and weighed out in 12.5 or 16 gram quantities and placed in glass vials with rubber stoppers, from which the air was evacuated or the air was replaced with CO_2 gas. Twelve and one half to 16 grams represent the average amounts of dried plasma obtained from 500 c.c. of blood. The small vial (120 c.c.) containing the plasma and another small vial (60 c.c.) containing pyrogen-free water can easily be carried in the coat pocket of a physician (figure 1). With the aid of a 50 c.c. syringe and needle any physician can have the equivalent of a pint of blood (excluding red blood cells) available at any moment. Such 4 or 5 fold concentrated plasma is popular because it can be administered within three to five minutes of time. The water used for the restoration of the dried plasma was obtained from an electrical Barnstead still; the water from the still passed through a Micromax conductivity indicating recorder, which rejects water having more than one part of foreign material in 75 million parts of water. With few exceptions (one of which will be described below) all of the plasma was adminis-

tered in the 4 or 5 fold concentration, i.e., 12.5 to 16 grams of dried plasma dissolved in 40 to 50 c.c. of pyrogen-free water. Less than a minute usually is required for the process of dissolving. The addition of 250 c.c. of water would be required to bring the plasma to so-called isotonicity or to the
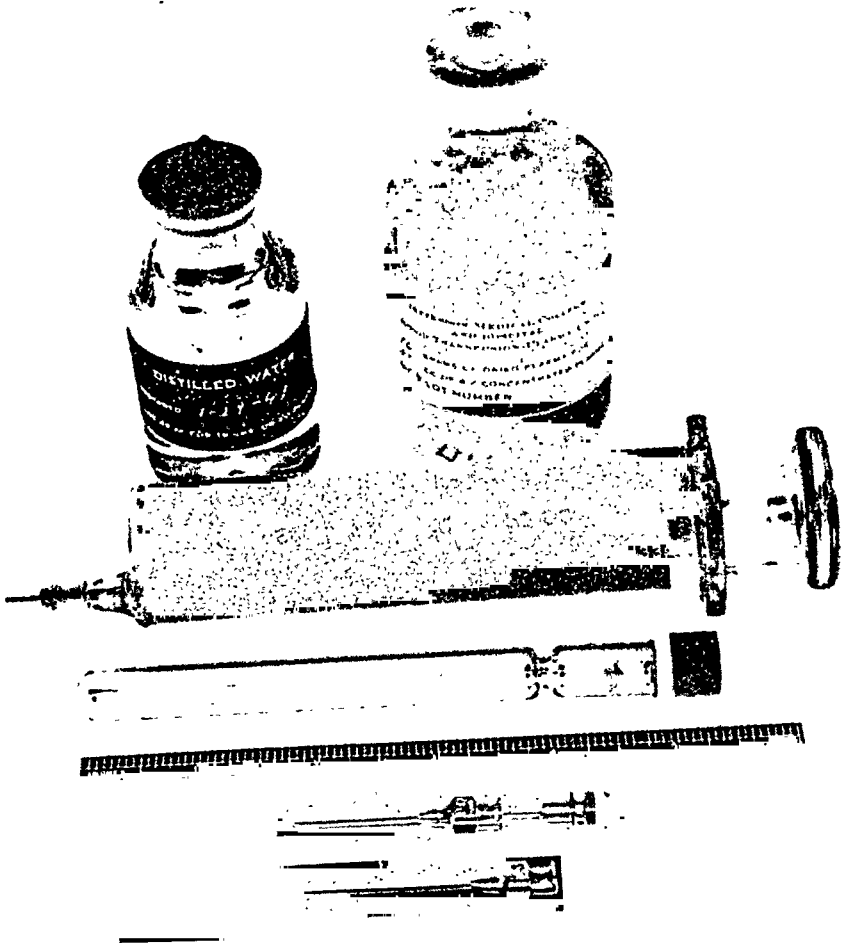
FIG. 1. The illustration shows 16 grams of dried plasma in a 120 c.c. vial, 50 c.c. of pyrogen-free distilled water in a 60 c.c. vial, a 50 c.c. syringe, a 20 gauge needle for intravenous administrations and a 20 gauge styletted needle for intrasternal administrations (18 gauge styletted needles are better for the latter because 4 fold to 5 fold concentrated plasma is quite viscid) with test tube container and rubber cap. The combined weight of the above articles securely wrapped in corduroy cardboard and heavy wrapping paper is one pound, and the package measures 8 by 4 by 2 inches. Unwrapping such a package, dissolving the plasma and administering it, can require as little as 5 minutes of time. It can be administered in fox holes or on rolling ships or ambulances. (Since our armed forces are well-supplied with medical equipment only the 120 c.c. vial with plasma need be shipped from this country. It weighs 160 grams.)

original fluid state. The pH of restored plasma without the addition of CO_2 varies between 8.1 and 9.3, but with the addition into the sealed bottle, before water is added, of 120 c.c. of CO_2 (the amount removed in the process of drying) the pH is brought down to 6.8–7.8. Those vials in which the air was replaced with CO_2 before storage did not need additional CO_2 to bring

the pH to 6.8–7.8. The CO_2 was obtained from small cylinders which can be found in any anesthetist's equipment.

	pH	Prothrombin (% of normal)
1. On collection from three donors. Fresh citrated blood	7.8	100
2. Four days later after separating and pooling of plasma (fluid)	7.8	75
3. Six days later after drying and restoring to original tonicity, with		
(a) H_2O	9.2	27
(b) H_2O and CO_2	7.5	43
4. Six weeks and one year after restoring dried plasma to fluid state (original tonicity) with		
(a) H_2O	9.0	30
(b) H_2O and CO_2	7.4	33

As can be observed the prothrombin levels dropped proportionally to time of storage before drying. Prothrombin of plasma does decompose on standing in the fluid state, but decomposes very slowly, if at all, in the dried state. Very little plasma prothrombin is lost if plasma is dried within 24 hours after removal from donor and if, when it is to be used, it is restored to the fluid state with water and CO_2 (in the amounts that were removed in drying—usually 60 vols. per cent or 60 c.c. per 100 c.c. of fluid plasma).

c. Transfusion Sites. Most of the blood transfusions were administered intravenously; however, many were administered by other intra-endothelial routes; through the intrasternal or intratibial marrow cavities. The corpus cavernosum of males, a site of transfusion suggested by Strain,[8] was used only once; it was successful. In cases of severe shock, or in children, or in very fleshy patients in whom veins were not palpable, or in cases of burns where veins were mutilated or in cases (of epileptics, or on board a rolling ship or ambulance, etc.) in which motion of arms or legs could not be satisfactorily controlled the other intra-endothelial routes became necessary. We have administered blood and both concentrated and diluted plasma intrasternally with the aid of syringes or by the "drip" method. Craver[9] pointed out that the first diagnostic sternal aspiration was done by Mosler in 1876. This site has been used extensively for aspiration[10] and injection purposes[11, 12] since.

d. Reactions Following Administration of Blood or Plasma. From patients who have reactions, the following information (on mimeographed sheets) is obtained:

Card No. of

Patient................Donor................Date................trans................
Age of Patient................Attending Physician ....Ward or Room............
Amount of blood received................Type of blood................
Diagnosis of patient................pre- or postoperative................
Complications................
    (pregnancy, abortion, pulmonary or hepatic disorders, malignancy or previous multiple transfusions)
Type of reaction (urticaria................Incompatibility................chill without
        fever................Chill with temperature rising so many degrees above
        pre-transfusion level ....

Temperature: Before...................... Pulse: Before...................... Resp.: Before......................
                During.................... During.................... During...... ....
                After...................... After...................... After......................
                After......................* After......................* After......................*
                After......................* After......................* After......................*
Blood pressure: Before................................ .... After..
                       Time............................... Time..

Pre-transfusion findings:

Course of disease (fever-free, septic, etc.)................... ....
Pre- or postoperative............................ ....
Type of operation (difficult......................, prolonged......................., severe....... ....)),
               hemorrhage......................................, etc..........................
Number of transfusions previously administered and date of administrations ....
....
Had morphine or atropine been given before transfusion.......................................
Had patient been receiving "sulfa" drugs..........................., if so what was the last blood
level before transfusion.......................... ...date of level................. ....
Was patient nervous before and during transfusion....................................
Was patient in circulatory collapse................ ... .
Condition of heart.......................................diagnosis...............................
Conditions of lungs..
Was there a dry cough............................ ....
Was there difficulty in inserting the needle (pain, etc.)............................
Was there "water of condensation" in tubing of transfusion set..........................
How long previous to transfusion had transfusion set been sterilized......................
Was cellulose tubing used.......................................

Findings during transfusion:

Time of transfusion (a.m. or p.m.).................................. ... .
Changes in color of skin...... ....
Presence of urticaria................................ .. ..
Did patient shake...
Did patient complain of chilliness............................. ....

Laboratory data:

    (a) Before transfusion—
Hgb. for several days, weeks or months previous to transfusion.........................
Van den Bergh................. ....
Urine analysis.. pH..............................
    (b) After transfusion—
Time interval after reaction when temperature returned to pre-transfusion level................

Results of recrossmatch..
Titer of blood given (Anti-A and Anti-B)................................
Rh agglutinogen determination.......................................
Hemoglobin { before transfusion.......................................
             immediately after transfusion.......................................
             24 hrs. after transfusion.......................................
Spectroscopic examination of { Plasma   for   { oxyhemoglobin
                            { Urine   { methemalbumin

Urine:

Acidity of urine..
pH..

* In column marked "after"—indicate time in minutes or hours.

Urobilinogen level..

Hematin crystals and casts...

Time collected after transfusion..

Characteristics of citrated blood administered:

How old was blood...had it been frozen.........................

Had blood stood in room long before administration...

Amount of hemolysis..was blood shaken violently.............................

Presence of chylomicron or fat...

Was blood free of clots and properly citrated...

Technic of administration:

How fast was blood given, amount of blood and interval of time...........................

Was metal filter plugged...

Were other fluids or therapeutic agents being given at the same time....................

Was patient kept warm during transfusion...

Donor:

Did donor have a 'cold' or infection or other physical dysfunctions.......................

If patient was retransfused was the same donor used...

COMMENTS:

....

....

....

RESULTS

During the year there were 3,906 donors (3,808 gave approximately 500 c.c., and 98 gave approximately 250 c.c. of blood) from whom were withdrawn 3,857 bottles of blood each of approximately 500 c.c. quantities. The blood was dispensed as follows:

2,571 bottles {
  2,397 transfusions of 500 c.c. each
  214 transfusions of 250 c.c. each
  258 transfusions averaging 130 c.c. each
  _____
  2,869 transfusions
}

1,177 bottles from which the plasma was centrifuged or separated and then dried (Hill Adtevac process)

109 bottles destroyed or otherwise used (breakage 30, positive serologic test 71, and research 8). 1.8 per cent of the donors had positive Wassermann or Kahn tests. Although it is well known that spirochetes can not survive more than 48–72 hours in cool (35° F) citrated blood, such blood was discarded.

_____

3,857 bottles

The 2,869 transfusions were given to 1,089 patients (897 receiving blood only and 192 receiving both blood and restored dried plasma). Three hundred fourteen patients (192 receiving both blood and restored dried plasma and 122 receiving only restored dried plasma) were given dried plasma as follows:

316 infusions of 16 gm. of dried plasma restored in 50 c.c. pyrogen-free distilled water.
344 infusions of 12.5 gm. of dried plasma restored in 40 c.c. pyrogen-free distilled water.
 35 infusions of 2 to 11.5 gm. of dried plasma restored in various quantities of pyrogen-free distilled water.

——— .

695 infusions of plasma. Practically all of the plasma infusions were administered as 4 or 5 fold concentrated plasma or the dry product restored to one-fourth or one-fifth of its original fluid volume.*

Two hundred and sixty-one units (16 gm. each) of plasma were dispensed elsewhere and 200 units were on hand at the close of the year, accounting for the approximate 1,150 units produced during the year. A few units were used for research purposes.

Blood Transfusions

The transfusions, arranged according to International typing nomenclature, to quantity per day and to services of the hospital, follow:

Type of Blood	No. of Transfusions		Services	No. of Transfusions
"O"	1,308		Priv. and semi-priv.	721
"A"	1,067		Women's Surg. Wd.	454
"B"	334		Men's Surg. Wd.	418
"AB"	160		Gynec. Wd.	256
	———		Men's Special Wd.	205
	2,869		Men's Medical Wd.	205
			Women's Medical Wd.	146
No. of Patients	Amount in One Day		Maternity Wd.	189
			T.B. Wd.	75
1	2,000 c.c.		Children's Wd.	54
4	1,500 c.c.		Urology Wd.	33
2	1,250 c.c.		Miscellaneous	113
66	1,000 c.c.			———
8	750 c.c.			2,869
536	500 c.c.			
214	250 c.c.			
258	10 c.c. to 200 c.c.			
———				
1,089				

The greatest quantity of blood administered to any one patient in 24 hours from this Transfusion Unit was 2,000 c.c. Most transfusionists feel that that quantity is a maximum, but when blood is needed there probably is no maximum quantity. Wiener and Pennell[13] have given 5,000 c.c. of blood to one patient in 24 hours. One patient (M. L., carcinoma of cervix) had 46 transfusions (the largest number given to any one patient), another (J. P., bleeding peptic ulcer) had 36, and another (J. B., hypoplastic anemia) had 32 of 500 c.c. each. These three patients were alive and well one year, three months, and six months respectively after the final transfusion.

Reactions to Transfusions

Total number of patients	1,089
Total number of transfusions	2,869
Total number of reactions (incompatibility, or associated with chills with or without fever, or urticaria)	94 (occurred in 74 patients)
Percentage of all reactions	3.2
Percentage of pyrogenic reactions	2.3

* By June 1, 1943 over 1200 administrations of plasma (the great majority as 4 or 5 fold) had been given; with the reaction rate less than 0.1 per cent.

The percentage of reactions is closely similar to those of other clinics.[14] There are those,[38] however, who feel that post-transfusional febrile reactions "cannot be reduced to a level lower than about 3 per cent," and that these non-specific reactions "are not caused by specific agglutinogens or antibodies, such as 'A' and 'B' substances or by isohemolysins, isoagglutinins, anti Rh substances and so on," but rather by pyrogenic substances in the intravenous apparatus or in the solutions used. Ninety-five per cent of the patients, 91 per cent of the transfusions and 100 per cent of the reactions, arranged according to diagnosis, follows (table I):

TABLE I

Diagnosis	Cases of Infections (Includes patients with or without surgical interference)	Medical Cases (Cardiovas. renal dis., arthritis, cirrhosis of liver, etc.)	Surgical Cases (Hysterectomy, hernia, E.N.T., etc.)	Cases of Anemias Prim. (Leukemia, purpura, etc.)	Sec. (G.I. ulcers, fibroids, etc.)	Cases of Malignancies (Includes patients with or without surgical interference)	Totals
No. of patients	251	96	413	36	33	211	1040
No. of transfusions	711	238	781	181	63	646	2620
No. of reactions	54	5	3	6	7	19	94
% of reactions	7.5	2.1	0.3	3.3	11.1	2.9	
% of pyrogenic reactions	5.6←	1.6	0.1	2.7	6.3	1.9←	

	No. Pts.	No. Trans.	Reactions No.	%		No. Pts.	No. Trans.	Reactions No.	%
G. I. Infections (Appendicitis, peritonitis, cholecystitis, colitis, etc.)	59	174	9	5.1	G. I. Malignancies	122	367	6	1.6
Resp. Infections (Bronchiectasis, lung abscess, empyema, etc.)	57	236	13	5.5	Resp. Malignancies	22	59	5	8.4
Gyn. Infections (Pelvic infl. disease, infected abortions, puerperal sepsis)	42	98	12	12.2	Gyn. Malignancies	26	99	1	1.0
	158	508	34 av. 6.6%			170	525	12 av. 2.2%	

Pyrogenic reactions following transfusions arranged according to frequency and diagnosis:

Gyn. infections 12.2%
Respiratory mal. 8.4%
Second. anemias 6.3%
Respiratory inf. 5.5%
G. I. infections 5.1%

If pyrogenic reactions are due exclusively to foreign proteins such as bacteria, etc. in the equipment used for administering transfusions, one would feel that the distribution of reactions would be approximately equal regardless of diagnosis.

CASE REPORTS OF REACTIONS TO BLOOD TRANSFUSIONS (table 2)

The 94 reactions, which occurred in 74 patients, arranged according to type and diagnosis, follow:

TABLE II

Type of Reactions	Infections					Malignancies					Anemia		Medical		Surgical			Totals
	G.I.	Resp.	Gyn.	G.U.	Med.	G.I.	Resp.	Gyn.	G.U.	Misc.	Pri.	Sec.	G.I.	G.U.	G.I.	Gyn.	Neu.	
1. Chill but no elevation of temperature	2	2	1	1	1	3	1			1	1	2				1		16
Chill with fever of—																		
2. 1°	2	1	2		1	3	3				1	2	1		1			17
3. 2°	5	7	9	1	4	1	1				2	2	1	1				34
4. 3°	2	1	1			2	1				1		1					9
5. 4°		4						1			1							6
6. Urticaria	3	1	2			1						1	1				1	10
7. Incompatibility	1													1				2
Totals	15	16	15	2	6	10	6	1	1	1	6	7	4	1	1	1	1	94

a. Chills without Fever. Of the 94 reactions following transfusions of blood, little can be said of those (total of 16) in which the patients complained of chilliness without an associated elevation of temperature. Apparently no harm occurred to the patients. However, it has been noted that in several patients with fever, the temperature will become normal during the transfusion and remain normal thereafter. The following is a case in which this occurred: K. McG., acute pyelitis, had fever of 103° F. at start of the transfusion. Hemoglobin level was 55 per cent at that time. During the transfusion of 500 c.c. of citrated blood the temperature became normal, but the patient became very chilly, his teeth chattered and his arms and legs shook. Patient remained free of fever for three days. Hemoglobin level was 59 per cent, 24 hours after the transfusion.

b. Chills' with Fever (Pyrogenic Reactions). Of the 66 reactions associated with various degrees of elevation of temperature, in only five instances (M. C.—bronchiectasis and myocarditis, J. H.—carcinoma of the esophagus, G. S.—acute lymphoid leukemia and J. J. and I. M.—secondary anemia due to bleeding fibroids) did reactions with hemolytic aspects occur. These were determined by an increase in urinary urobilinogen levels; no clinical jaundice or hemoglobinuria was observed in four of the cases. Despite the increase in urinary urobilinogen levels in two cases (M. C. and G. S.) an elevation of the hemoglobin levels occurred 24 and 48 hours after transfusion, over the pre-transfusion levels. None developed oliguria. All of the cases had had many transfusions previously. The case that did develop clinical jaundice follows:

I. M., with a secondary anemia due to bleeding fibroids, had type "A" blood. On 6–26–42, 500 c.c. type "O" blood were administered. This was one of the three instances of 2,869 transfusions when blood other than the type identical to that of the patient's was administered. The transfusion was started at 2:30 p.m. with temperature 99° F., pulse 86; at 4:00 p.m. temperature 99.9° F. and pulse 100; at 6:00 p.m. temperature 102.3° F. and pulse 120. There was no significant change in respiration rate or blood pressure. At 11:00 p.m. temperature was normal again. The next morn-

ing the patient was mildly but distinctly jaundiced and the urine urobilinogen level had risen from 1 : 10 to 1 : 100, bile pigments were present in urine and the hemoglobin level did not change (50 per cent before and 50 per cent 12 and 24 hours after transfusion). The urine was very 'acid' before and after transfusion. It was felt that the reaction was due to the fact that the anti-A titer of the donor's blood was 1 : 512. Klendshoj et al.[15] feel that anti-A and anti-B titers of 1 : 100 or over are very dangerous. Aubert et al.[5] do not agree that such titers are dangerous; they believe that titers over 1 : 512 may be harmful, however.

Klendshoj et al. suggest that A or B specific substance be added to bring the anti-A and anti-B titers down to 1 : 2 or thereabout before "O" blood is administered. They feel that small Blood Banks can be operated successfully on only "O" blood if A and B specific substances are used. It is not yet known whether the A and B specific substances, if given in too large doses, might be responsible for the development of dangerous antibody formation. This is not likely because the excess is probably neutralized or excreted.

An explanation for the other four hemolytic reactions could not be determined. The urine urobilinogen levels were 1 : 100, 1 : 200 and 1 : 400 (two cases), respectively.

We have, as have others,[16] observed that if cases that had had a febrile reaction (not hemolytic) following a transfusion were given more of the same blood a few hours later, no febrile reaction occurred and, furthermore, the post-transfusion hemoglobin levels rise proportionally to the total amount of blood given. Example follows,

M. C., colored female, aged 38, with diagnosis of bronchiectasis and myocarditis, had received 200 c.c. of a 500 c.c. bottle of citrated blood on February 6, 1942, when the patient developed a chill associated with an elevation of temperature to 102° F., and an increased number of râles in the chest. The transfusion was stopped; the remaining 300 c.c. of citrated blood were placed in the ice box for 16 hours, then readministered to the same patient without the occurrence of fever, without chills, and without an increase in the number of râles. The hemoglobin level just before the administration of the 200 c.c. quantity of blood was 70 per cent; five hours after the administration of the 300 c.c. quantity it was 79 per cent; and 24 hours later it was 81 per cent.

We have had many cases similar to the one just described, but we also have observed the opposite sequence of reactions, as follows:

A. P., white female, aged 34, with diagnosis of ulcerative colitis, received 250 cc. of a 500 c.c. bottle of citrated blood on March 14, 1942, without reaction. Because of that fact, the remaining 250 c.c., which had been stored in the ice box, were administered the next day. It, however, was followed by a shaking chill which was associated with an elevation of temperature to 101° F. The hemoglobin level just before the first administra-

tion of 250 c.c. of blood was 47 per cent; four hours after the second 250 c.c. quantity it was 49 per cent; and 24 hours later 55 per cent.

In both cases just mentioned, each had had many transfusions before and after these specific instances without reactions, and to the best of our opinion, no significant changes either in the citrated blood or the clinical condition of the patients could account for these febrile reactions. One might say that the first case developed an immunity, or that all of the reactive agents producing the febrile reaction were consumed during the first transfusion; and in the second case the second 250 c.c. quantity of blood had become excessively hemolyzed or altered. The only conclusion, theoretical in nature, that we could reach was that the reactions were possibly due to reactive circulating proteins of the recipient possibly derived from the food eaten or from the infected lesions present in the body. Masor and associates [17] demonstrated that in dogs harmful reactions occurred most frequently when the donor had been fed a protein or carbohydrate-protein meal and the recipient had been fasting. A week later A. P., the case last mentioned, was given 250 c.c. of a 500 c.c. bottle of citrated blood on March 24, 1942, and the remaining 250 c.c. on March 25, 1942, without reactions following either transfusion. Such "divided" transfusions have been given to many patients without reactions following either transfusion (L. H. (3–11 and 3–12), J. M. (3–14 a.m. and 3–14 p.m.), J. D. (5–14 and 5–15), H. C. H. (5–4 and 5–6), J. B. (6–11 and 6–12), and J. C. (7–24 a.m. and 7–24 p.m.), etc.).

c. *Urticaria.* Little need be said about the 10 cases that had urticaria. All responded satisfactorily to adrenalin. The donors had not eaten for a period of at least three hours before donating their blood. However, it is generally assumed that all cases of urticaria are due to an allergic sensitivity to the donor's blood or its contents. None of the 10 cases developed an elevation of temperature. The transfusions were not stopped when urticaria developed and the urticaria did not progress in severity, indicating that all of the reactive antibodies had been consumed or combined during the administration of the first few c.c. of donor's blood. Two hundred fifty c.c. of a 500 c.c. bottle of blood of one donor (F. K., 7–29–42) were given to a patient (A. G., gastric carcinoma) who developed severe urticaria, whereas the remaining 250 c.c. were given to another patient (H. H., abortion) within 12 hours' time of the first transfusion without the slightest evidence of an urticarial reaction.

d. *Incompatibility.* 1. A and B agglutinogens: There were two patients who suffered reactions due to incompatibility. One was due to sheer negligence of the ward administrator because all of the bottles were and are plainly labeled. Blood of group B was given to patient of group A. However, the patient had received but 25 c.c. of blood when this was discovered. He suffered a shaking chill with elevation of temperature but he did not develop hemoglobinuria. According to Oehlecher,[18] at least 80 c.c. of blood

must be hemolyzed before hemoglobinuria will occur in an adult. The other case of incompatibility brought out two interesting features, and follows:

R. R., 48 year old male from whom a gangrenous appendix was removed on August 20, 1941, in another hospital, was typed elsewhere as a "B" and was given 500 c.c. of "B" blood on three occasions (August 22, August 24, and August 26) without reactions. Under unusual circumstances a bottle of "B" blood from this Transfusion Unit was sent to the other hospital on September 4, 1941. (This has been the only occasion that blood has been sent outside of Jefferson Hospital or associated departments.) A non-centrifuged cross-match was watched for 10 minutes and no agglutination occurred on 'either side of the slide.' After 10 or 15 c.c. of blood had been administered, the patient developed dyspnea, hyperpnea, circulatory collapse, muscular incoördination and became irrational; he did not have headache, backache, or chills. After obtaining high titered serum it was found that the patient's blood was type "O," and that 30 minutes of time had to elapse before the cells agglutinated on re-cross-matching (slide method). The patient had built up antibodies against "B" cells following the three transfusions of "B" blood, and on September 4, 1941, the titer of the patient's serum for "B" cells was 1:1024, for "A" cells, 1:32. On September 11, 1941, serum of the patient agglutinated "B" cells in dilutions of 1:4096. The patient was discharged well on September 24, 1941.

This case illustrates that antibodies were not formed in sufficient numbers to cause a reaction after the first three transfusions. However, after a lapse of 10 days, the antibody concentration rose to dangerously high levels and some 20 days later to exceptionally high levels. The other unusual feature in this case was the delayed agglutination on cross-matching by the usual standard 'slide' technic. We have had three patients (R. E.—Cooley's anemia, R. R.—post-appendectomy, and J. H.—carcinoma of esophagus) who had delayed or retarded agglutination (slide method) on cross-matching of 11 mins., 30 mins. and 35 mins., respectively. The period of delay can be essentially eliminated by centrifuging. The Landsteiner technic is the only safe technic of cross-matching.

2. Rh agglutinogens: There are three types of Rh agglutinogens—Rh_1, Rh_2 and $Rh_{1 \text{ and } 2}$.[4b] In all cases that had multiple transfusions, or that were pre- or post-delivery or abortion, determinations were made for the presence or absence of the Rh agglutinogen [4b] in the red blood cells. Of the 74 patients that had reactions (94 reactions) Rh tests were made on 48 patients— all were Rh positive. Of four mothers, who delivered very jaundiced babies, three (mothers of C. D., R. R. and B. H.) were Rh negative. Only plasma was administered to these mothers post-delivery. The babies spontaneously overcame their jaundice.

The Rh antibodies that developed in the serum of R. R.'s mother were of the Rh_2 variety and the titer reached a level of 1:512 three weeks after delivery. The titer was 1:256 six months after delivery.

We had one patient (E. K.) who had purpura and had had many transfusions and who said that she had a febrile reaction every time she had a transfusion except when her mother was the donor. It was then learned that both she and her mother were Rh negative—or rather the red blood cells of the patient and her mother did not contain the Rh agglutinogen—thereby probably explaining the absence of reactions.

3. Cold agglutinins. There was one case (E. B.—rheumatic fever) that had marked concentration of cold agglutinins. At room temperature agglutination was still present in dilutions of 1 : 1,280.

DISCUSSION OF REACTIONS FOLLOWING BLOOD TRANSFUSIONS

The data collected from the mimeographed sheets (copies are shown in the section on technic) on all the 94 reactions could not be presented in such a short discourse and only general conclusions can be discussed. As pointed out previously, the majority of reactions occurred in the cases with infections, followed by those with malignancies and with secondary anemias.

Of the infections, the gynecological cases had the highest percentage of reactions and of the malignancies, the respiratory cases had the highest percentage of reactions. One interesting finding which may or may not have any significance was the fact that of the 94 reactions, 88 followed transfusions that were administered in the afternoons or early evenings. Since much of the interns' mornings are taken up in making rounds and in assisting in operating rooms, most medications are given in the afternoons. However, it is known that in the afternoons the temperature of the average person is highest and, too, it is known that patients with tuberculosis and other pulmonary infections have elevations of temperature in the afternoons. It may be possible that human beings are more sensitive to pyrogens in the afternoons. Probably less than 66 per cent of the 2800 transfusions were given in the afternoons.

Many transfusions were given just before, just after or during the administration of other medications. In this hospital, 0.94 per cent of patients given 5 per cent glucose and saline solutions (obtained elsewhere) develop pyrogenic reactions. Therefore, a certain percentage of reactions attributed to transfusions are due to such solutions. Other observers [14] have shown that saline and dextrose infusions are responsible for as much as 2.8 per cent of pyrogenic reactions in an average hospital. Whether these solutions contain pyrogens or are given so fast and in such quantities, that slight myocardial decompensation or pulmonary edema develops, is not known. Men with large direct transfusion experiences (as De Bakey [19] and one of us, H. W. J.) rarely encounter "speed shock"; however, in cases with poor myocardial tone all intravenous fluids should be given slowly (60 to 170 drops per minute). Riddell [20] strongly emphasizes that all transfusions should be given slowly, and states "the slower the transfusion the less likely a rigor will occur." Whitby [21] has indicated that in cases of cachexia,

cardiac disorders and respiratory embarrassment the rate of the transfusion should be between 0.5 c.c. and 1 c.c. per lb. of body weight per hour. This rate permits the circulatory system to adapt itself to the increased fluid volume.

In the majority of the pyrogenic reactions the temperature of the patient returned to the pre-transfusion levels within three hours, rarely later than 10 hours. Of course, it is well known that many patients with infectious processes have chills and fever that last two to 12 hours without transfusions or any other medication. Such may be due to lack of "resistance" (depletion of adrenalin, etc.), but more likely are due to sensitivity to some reactive foreign protein that has escaped into the blood stream. In cases with infectious and malignant processes, foreign bacterial and cellular proteins circulate; in obstetrical patients, fetal foreign proteins circulate; in postoperative cases in which many small vessels are thrombosed, foreign proteins of clotted blood circulate; after eating food, foreign 'food' proteins circulate. Also, bacterial or fungal foreign proteins present in unclean tubing or "old" distilled water, or sterilized denatured blood in unclean needles or bottles can be injected during a transfusion. Since most pyrogenic reactions are very similar, if not identical, with those seen following serum shock, foreign proteins are probably the most likely responsible agents in post-transfusion febrile reactions. Whitby[21] states, "simple pyrexial reactions are most commonly due to foreign protein, dead bacteria, disintegrated or intact and living but non-pathogenic bacteria; all of these may be found in improperly prepared or stale distilled water, improperly prepared solutions and dirty apparatus."

To reduce the percentage of post-transfusion reactions, the following cautions might be mentioned:

1. In typing blood, use high titered typing sera (which can be prepared [22]) and be aware that perhaps 25 per cent of such sera have high concentrations of hemolysins. Use the centrifuge-Landsteiner technic. Type for subgroups A_2 and A_3.

2. In cross-matching use the centrifuge. If the slide technic is used, wait 30 minutes or more to avoid delayed or retarded agglutination. If "O" blood is used it is probably wise to add A and B specific substances to bring the anti-A and anti-B titers below dangerous levels.[15] Homologous blood is safer.[5]

3. In all post-partum or abortion cases or cases that have had previous transfusions determine the presence or absence of the Rh agglutinogen in the red blood cells of the patient. If Rh negative, use Rh negative donors. (O Rh neg., A Rh neg., B Rh neg. and AB Rh neg.)

4. Use fasting donors who are without infections, such as infected teeth, tonsils, sinuses, fistulas, etc., and are free of syphilis, malaria, filariasis, influenza, etc.

5. Use meticulously clean apparatus. Brush inside of all tubing with weak sodium hydroxide solution. Clean needles, especially inside of hilt, with swabs dipped in hydrogen peroxide. Rinse all apparatus with pyrogen-free water and sterilize immediately after rinsing, to avoid possibility of bacterial or fungal growth. All solutions should be prepared from freshly distilled pyrogen-free water. Cellulose tubing (Hospital Liquids Incorporated) has proved to be a very satisfactory agent in administering blood. It is discarded after once used. Properly prepared it is free of pyrogens.

6. Use only well citrated and filtered (metal filters are preferable) blood. Do not store for more than 4 to 10 days. Keep blood cold and at a constant temperature (35° F). Low temperatures retard the clotting mechanism and prolong the life of red blood cells. Administer blood cold. Do not shake blood. Have pressure in bottles containing blood, near atmospheric pressure during storage.

7. In the technic of administering transfusions, preferably have urine of patient alkaline. However, Brainard [23] has shown that pyrogenic reactions occurred even if urine is alkaline. It is preferable to give a sedative or morphine 30 minutes before a transfusion. Have adrenalin available. It is also preferable to administer transfusions in the mornings, and if possible when the temperature of the patient is near normal levels. If possible prepare transfusion apparatus outside of patient's room; have sharp needles and get into vein as quickly and as painlessly as possible. Use pyrogen-free solutions for all intravenous injections. Except in emergencies it is preferable to give blood slowly, i.e., 1 c.c. per lb. per hour. Dosage of blood depends upon many conditions:

1. Degree of anemia (hemoglobin and hematocrit levels)
2. Degree of shock (plasma protein levels, etc.)
3. Level of blood pressure
4. Pulse and respiratory rate
5. Existence of myocardial and respiratory damage.

One should give that quantity of blood that will improve and maintain the blood pressure readings, and the quality and rate of the pulse to near-normal levels associated with a return of normal color of skin, etc. Massive transfusions (5,000 c.c. or more in 24 hours) are often required under war conditions. Clinical observation must be constant and critical, to determine adequate dosage.

No one knows why a transfusion is considered "a pint" except that "a pint of blood" can usually be removed from a normal person without harm. Marriott and Kekwick [24] have devised a fairly reliable guide for dosage of blood as follows:

$$\frac{\% \text{ of rise of hgb. required}}{100} \times \text{Patient's normal blood vol. in c.c.} = \text{The vol. of blood in c.c. to be transfused.}$$

There are approximately 40 c.c. of blood per pound of body weight in the normal individual. Example: 120 lb. man with hemoglobin level of 50 per cent requires a hemoglobin level of 70 per cent—20/100 × (120 × 40) = 960 c.c. of blood to be transfused in order. to raise the individual's hemoglobin level to 70 per cent.

It probably never will be possible to prevent the pyrogenic reactions, following transfusions which may be due to fetal, malignant, nutrient (food), cellular, or bacterial foreign proteins circulating in the patient. However, it is possible to give blood without reacting agglutinogens or agglutinins. Such blood can be prepared in three ways:

1. Place "O" Rh negative red blood cells in "AB" plasma.[25]
2. Place "O" Rh negative red blood cells into pooled plasma.
3. To each of 500 c.c. of "O" Rh negative blood add A and B specific substance (25 mg. and 10 mg. respectively).[15]

PLASMA INFUSIONS

One thousand one hundred seventy-seven "outdated" bottles of blood (611,295 c.c) were centrifuged or separated and the plasma (295,930 c.c.) was removed.

This liquid plasma had the following characteristics:

```
Age................. 10 to 14 days old (after withdrawal from donors).
Hemoglobin.......... 60 to 150 mg. per cent.
Solids.............. 7.9 to 8.4 gm./100 c.c.
Total Protein....... 5.4 to 7.1 gm./100 c.c.
Fibrinogen.......... .21 to .34 gm./100 c.c.
Prothrombin......... 40 per cent to 80 per cent (per cent of normal blood
                        immediately drawn from vein).
```

The liquid plasma was frozen in large glass ampoules and by the "Adtevac process" 18,219 grams of dried plasma were obtained (or 1 gram of dried plasma for each 16.2 c.c. of liquid plasma). The moisture content of the dried plasma varied from 0.3 to 1.0 per cent—the majority less than 0.5 per cent. When the dried plasma was restored to the original volume with distilled water, the pH varied from 8.1 to 9.3 and the prothrombin from 0 per cent to 27 per cent. If, however, CO_2 gas was injected into the rubber-stoppered vial before restoration to the fluid state the pH dropped to 6.8–8.0 and the prothrombin varied from 30 per cent to 50 per cent (see technic). The clotting time of restored plasma with water alone varied between 9 and 30 minutes; with water and CO_2—three to nine minutes.

The dried plasma was stored in paraffined rubber-stoppered glass vials of 120 c.c. capacity under vacuum or the air replaced by CO_2. After 12 months under these conditions the restored plasma had the same characteristics as those just described. About 1 gram of sodium citrate (the amount used to citrate the blood on withdrawal) was present in each 12.5 or 16 gram vial of plasma.

Sixteen grams of dried plasma restored to fluidity with 50 c.c. of distilled water (5 fold concentrated), given intravenously, will almost always cause a rise in blood pressure.[26, 27, 28] Of 68 patients with various diagnoses, the blood pressure rose (from 10 to 50 mm. Hg systolic and 5 to 30 mm. Hg diastolic) in 56, within 15 to 45 minutes after administration of the concentrated plasma. In the other 12 the blood pressure was unchanged. In 14 patients (postoperative shock, nephrosis, nephritis and ulcerative colitis), the blood pressure, the per cent of hemoglobin, the hematocrit and the plasma specific gravity were determined before, and 15 minutes and 1 hour after the administration of 50 c.c. of 5 fold concentrated plasma on 63 occasions. Only in three instances did the blood pressure fail to rise and in only three instances did the hematocrit and hemoglobin levels fail to become lower. The plasma specific gravity levels rose in all but ·11 instances. Similar findings have been reported by Hill et al.[4d] A typical example is seen in table 3.

TABLE III

Effect of Administration of Concentrated Plasma (intrasternally) (16 grams dried plasma dissolved in 50 c.c. water and administered 30 minutes after hemicolectomy).
Age of patient—57 years

	Blood Pressure	Hemoglobin (gm.)	Hematocrit %	Specific Gravity of Patient's Plasma
Before administration of plasma.........	98/52	10.1	37.0	1.0271
15 minutes after administration of plasma	125/62	9.7	35.4	1.0274
1 hour after administration of plasma.....	134/84	9.7	35.6	1.0280

Prothrombin levels were not changed in 12 patients after administration of 16 grams of plasma whether restored with water alone or with water and CO_2

As stated above, 4 and 5 fold concentrated plasma has been given intravenously most frequently, but in dozens of cases it has been administered intrasternally, essentially in cases of emergency when veins could not be found. Either concentrated or diluted plasma may be given most satisfactorily by this route.[42] In our experience of administering over 1200 infusions of concentrated plasma we find that severely dehydrated patients (exsanguinating hemorrhages in cases of ectopic pregnancy, placenta previa, post operation, etc.) apparently overcome shock more satisfactorily and quickly when first given concentrated plasma followed by saline infusions than when given isotonic plasma alone. Time is probably the significant factor.

Since the work of Post and Patek[47] who determined that 3.1 grams of albumin per 100 c.c. of plasma is the critical level for the formation of ascites in cases of cirrhosis of the liver, we have administered concentrated plasma to several patients with ascites (associated with cirrhosis of the liver) and with plasma albumin levels below 3.1 grams and have had startlingly encouraging results, such as complete disappearance of ascites. Such therapy, at the

present time, can only be considered as replacement therapy. The permanent effects are as yet unknown.

Reactions to Plasma Infusions with Case Reports. Six hundred ninety-five infusions of plasma were administered to 314 patients during the year. Well over 95 per cent of this number of infusions were given as the 4 or 5 fold concentrated solution. Only six reactions were observed in three patients.

J. S., a 44 year old male, was operated on for perforated duodenal ulcer on January 9, 1942 on which day he also received 25 grams of plasma (5 fold concentrated) without reaction. On January 17, 1942 and on January 20, 1942, 12.5 grams were given without reactions. On January 21, 1942, the patient developed slight dyspnea, slight tingling of fingers, and became beet red in color, associated with 1° rise in temperature and slight increase of pulse rate following administration of 12.5 grams restored plasma. This was not a typical reaction seen following transfusions. Fifty c.c. of 4 per cent sodium citrate were given intravenously and the same peculiar reaction occurred. On January 27, 1942 the patient received 16 grams of plasma without a reaction.

The reaction could not be attributed to the plasma in this case but rather to the citrate in the plasma.

D. L., a 9 year old male in the nephrotic stage of chronic nephritis, had generalized edema. On April 3 and April 14, 1942, by abdominal taps, 2,600 c.c. and 3,000 c.c. of ascitic fluid were removed. Sixteen grams of plasma were given on May 11, on May 14, on May 15, and on May 17, 1942 without reactions. Dr. K. Paschkis and one of us (L. A. E.) decided to administer antuitrin G in addition to the plasma in the hope that the proteins might be better retained.

On May 20, 1942, 16 grams of plasma were given intravenously with 5 c.c. of antuitrin G given intramuscularly. A pyrogenic reaction followed—temperature rose to 102° F. The same medications were given on May 21, 1942 followed by a severe pyrogenic reaction; temperature rose to 104° F. The same medication was given May 22, 1942 followed by a reaction and a temperature rise to 101° F. On May 23, 1942, 16 grams of plasma were given alone and no reaction occurred. On May 24, 1942, following both plasma and antuitrin, a reaction occurred. From that time on plasma and antuitrin were given on alternate days without reactions. The patient was discharged edema-free on June 10, 1942. Because of the excellent clinical results the same procedure was tried on two other cases of nephritis with edema (M. B. and E. H.). In neither case did reactions occur following simultaneous administrations of both plasma and antuitrin G. Excellent clinical results were obtained in all of the patients. In fact all three patients have been in clinical remissions for over eight months (February 1, 1943).

These four reactions can not be attributed to plasma but to the combination of plasma infusions and antuitrin injections. The explanation for the

reactions in the first case is most unclear since the other two patients did not develop reactions.

N. D., a 42 year old male, was operated upon for gangrenous appendix and streptococcic peritonitis on June 27, 1942. On the eighth postoperative day, 16 grams of plasma restored in 200 c.c. of distilled water were poured into 1,000 c.c. of saline and administered intravenously without reaction. When this procedure was repeated on the next day the patient developed a severe shaking chill with a 4° rise in temperature.

This reaction might have been due to the saline; or the plasma proteins with the saline might have formed a proteinate salt to which the patient was sensitive, or the intravascular osmotic pressure may have been raised to such levels as to absorb some bacterial proteins into the blood stream. We recommend that plasma always be given in the concentrated form unless the patient is definitely dehydrated.

Discussion of Reactions. Of the six reactions only the last one might be attributed to the plasma per se. So out of 695 administrations there was one reaction—a reaction rate of 0.14 per cent. This percentage is even lower than that of Hill et al.[7] We have noted that some patients complain of vasospasm of the injected vein when injecting 5 fold concentrated plasma with the pH above 8.5. By adding CO_2, which brings pH of the plasma down to 7.5 or less, vasospasms usually cease.

Discussion of Plasma. Albumin,[29] serum [30, 31] and plasma are available either in the liquid or desiccated state and all are satisfactory therapeutic agents for:

1. Overcoming shock
2. Restoring blood volume
3. Overcoming protein deficiency,[32] and
4. The constitutional treatment of burns.

a. *Albumin.* Cohn [29] precipitates albumin from human plasma by use of alcohol-water mixtures. Nearly two-thirds of human plasma is made up of albumin, which is responsible for the great majority of the osmotic pressure exerted by blood. (Albumin has a smaller molecular size than globulin.) Albumin may be desiccated and restored to a 4 or 5 fold concentrated solution or to the original fluid (isotonic) state by buffered saline. Four or 5 fold concentrated plasma will give the same experimental and clinical results that 4 or 5 fold concentrated albumin does [33, 34] and such plasma is much cheaper. Janeway [4c] feels that it will be possible in the future to purify bovine albumin so as to be in general use since it seems to be a relatively poor antigen in man. Others [35, 36] are trying to despeciate horse albumin successfully. However, if non-human albumin fails to become a commercial product there is an unlimited amount of human cadaver blood at all undertaking establishments from which human albumin could be commercially produced. Denaturation of the albumin should not be marked, because the Russians have been using cadaver blood successfully for transfusions for years.

b. *Serum.* There is considerable discussion as to the superiority of serum versus plasma in the treatment of shock. If properly prepared both are very effective. However, serum does not contain fibrinogen, beta globulin, prothrombin, etc., but does contain many breakdown products which appear when blood clots, including possibly denatured proteins which may have antibody-forming potentialities. Since serum has no particular advantage over plasma, our laboratory has concentrated its efforts on plasma. Of course, allowing the blood to clot after withdrawal does not permit its use for transfusions. Our experience has been limited to the use of restored dried serum in 4 or 5 fold concentrated solutions; however, we have used it in several cases with satisfaction. It can be used in most instances wherever plasma is indicated.

c. *Plasma.* Sturgis [37] said that ultimately dried plasma will be the agent universally used in the treatment of shock.

Plasma is usually a by-product or can be prepared from "out-dated" blood banks. The plasma can be removed from the red blood cells by centrifugation, aspiration or separation. If specimens of *blood* are pooled (10 parts group "O" blood to one of "AB" and one part each of "A" and "B" [28]) before the plasma is removed, the titers of the anti-A and anti-B agglutinins of the resulting plasma are usually reduced to extremely low levels, but if the various specimens of *plasma* are pooled the titers rarely get above 1:20 for either anti-A or anti-B.[38] Aubert et al.[30] have shown that although 99 per cent of the A and B specific substances exist in the red blood cells, 1 per cent of these substances exist in the plasma, which helps to explain how pooling of *plasma* can reduce the titer of the anti-A and anti-B agglutinins. Aubert et al.[5] have also shown that there is little danger of dangerous reactions even if these titers are as high as 1:512. No typing or crossmatching is necessary when pooled plasma is given—neither are skin tests needed or indicated.

Plasma can be made available in many ways such as:

1. *Isotonic Plasma Diluted with Equal Parts of Saline.* White et al.[40] feel that such a mixture is valuable in markedly dehydrated patients who are in mild shock. Concentration of urine usually gives some clue to the degree of dehydration (if kidneys have not been damaged or if patient has not lost significant quantities of salts); and most authors feel that specific gravity values above 1.012 indicate degrees of dehydration.

Such diluted plasma may be stored at room temperature or at 35° F. but there is always the danger of contamination.

2. *Isotonic Plasma.* If liquid plasma is stored at room temperature or at 35° F., flocculation, contamination and autolysis with denaturation of proteins can occur. Heath and Province [41] have clearly shown that they could not recommend merthiolate or "sulfa" drugs for the preservation of stored liquid plasma, and flocculation is a serious disadvantage, too.

3. *Frozen Plasma.* The necessity of low temperature ice boxes, the time required for thawing (30 minutes for 500 c.c.) and the serious clinical con-

sequences of thawing too rapidly are distinct disadvantages associated with the use of frozen plasma.

4. *Dried Plasma.* It is the most practical form of plasma. It is clinically as effective as dried albumin and cheaper.

a. It can be stored at room temperature for years.

b. It is compact and easily transported. Sixteen grams of dried plasma (the amount obtained from 500 c.c. of blood) takes up less space than that taken up by two golf balls. A 120 c.c. vial (see figure 1) which is 4.5 inches tall and two inches in diameter, and which contains 16 grams of plasma weighs approximately 160 grams. The plasma, a 50 c.c. vial of distilled water, and a 50 c.c. syringe with needles placed in a firm mailing tube weigh 16 oz. (1 lb.). A package wrapped securely in corduroy cardboard and heavy wrapping paper measures approximately 8 by 4 by 2 inches. To most of our armed forces, only plasma need be shipped because medical supplies and freshly distilled water are available at all except the front line aid stations. Frequently newspaper photographs taken at the battle fronts show wounded men receiving plasma by old-fashioned drip bottles hanging from trees, etc., and long, unwieldy tubing. This can be eliminated by administering the same quantity of plasma quickly and conveniently in the concentrated form with a syringe.

c. It has flash solubility. Sixteen grams of dried plasma will dissolve in 50 c.c. of water in one minute of time, making 4 or 5 fold concentrated plasma. Two hundred fifty c.c. of water would be required to restore that quantity of plasma to its original volume.

d. The restored plasma is not altered significantly in any known way. Scudder [4e] after making electrophoretic studies feels that plasma dried from the frozen state (Adtevac and others) is superior to those in which heat is used during desiccation. If CO_2 is added to plasma before restoration to fluid state very little prothrombin is lost (see technic). Prothrombin is not an important factor in treatment of shock anyway.

	Fluid Plasma (citrated)	Same plasma dried and restored to original volume with distilled water	
		24 hrs. later	6 mos. later
Total Protein (grams per 100 c.c.)	6.0	5.8	6.0
Albumin (grams per 100 c.c.)	4.2	3.9	
Globulin (grams per 100 c.c.)	1.9	1.6	
Fibrinogen (grams per 100 c.c.)	.28	.27	.24
Hemoglobin (mg. per cent)	25.0	25.0	25.0
Clotting time (minutes) upon recalcification	5.0	10.0	10.0

e. Dried plasma can be restored to any concentration desired, 10 fold, 5 fold, 4 fold, 2 fold, isotonic or diluted (with saline), etc. Ten fold is used in cases of nephrosis, 4 fold in shock and isotonic and diluted in dehydrated

patients (urine specific gravity 1.030 or so) requiring increased fluid volume as well as blood proteins. In patients with severe shock concentrated plasma should be used first (so that both interstitial and intracellular fluids are returned to the blood stream) and continued at least until the blood pressure is restored to near normal levels, then isotonic or even diluted plasma could be given. Of course, each case of shock is a law unto itself, and must be treated accordingly.
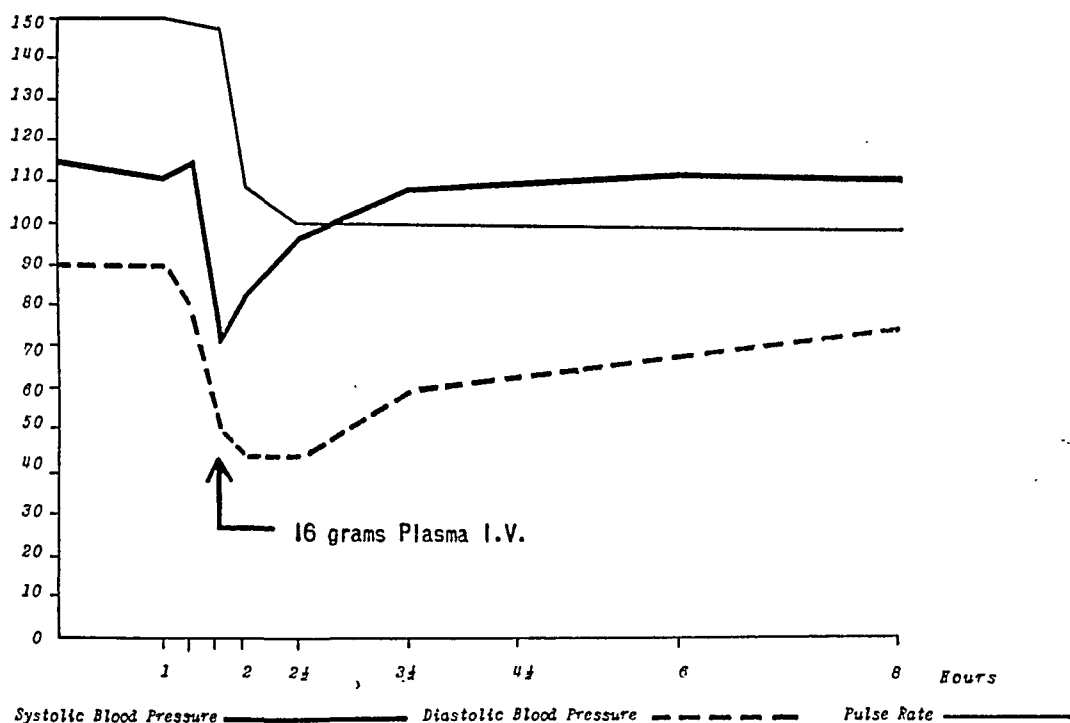
FIG. 2. Changes in systolic and diastolic blood pressure levels and pulse rate in a case of post partum shock following administration (intravenously) of *concentrated plasma* (16 grams in 50 c.c. distilled water).

f. Restored dried plasma is easily administered in any concentration. It does not require typing since it is made by the desiccation of pooled liquid plasma. Four fold concentrated plasma (dried plasma restored to one-fourth its original fluid volume) can be given intravenously or by other intraendothelial routes (see technic). To give it intrasternally insert a styletted needle (18 or 20 gauge, one inch long—an ordinary spinal puncture needle shortened to one inch in length) into the midline of the sternum at the level of the second interspace, point of needle directed cephalically at a 45° angle.[42] With aid of a 50 c.c. syringe, "one pint of blood" proteins can be given within 5 to 10 minutes, by this route. When plasma has to be given on a rolling battleship, in a fox hole, or in an ambulance, one can not resort to long rubber tubes and dripping bottles. In well over 1,200 administrations of 4 fold concentrated plasma we have never needed to filter concentrated plasma before administration.

g. Hemodilution followed the single injection of 50 c.c. of 4 fold concentrated plasma in 60 of 63 administrations. The blood pressure almost invariably rises following the administration of concentrated plasma either intravenously or intrasternally (see figures 2 and 3). The effects just described occur just as rapidly following administration intrasternally as intravenously.

h. Reactions are few, following administration of concentrated restored plasma. In 695 administrations the reaction rate was 0.14 per cent. Hill[7] likewise had less than 1 per cent reactions in his series.
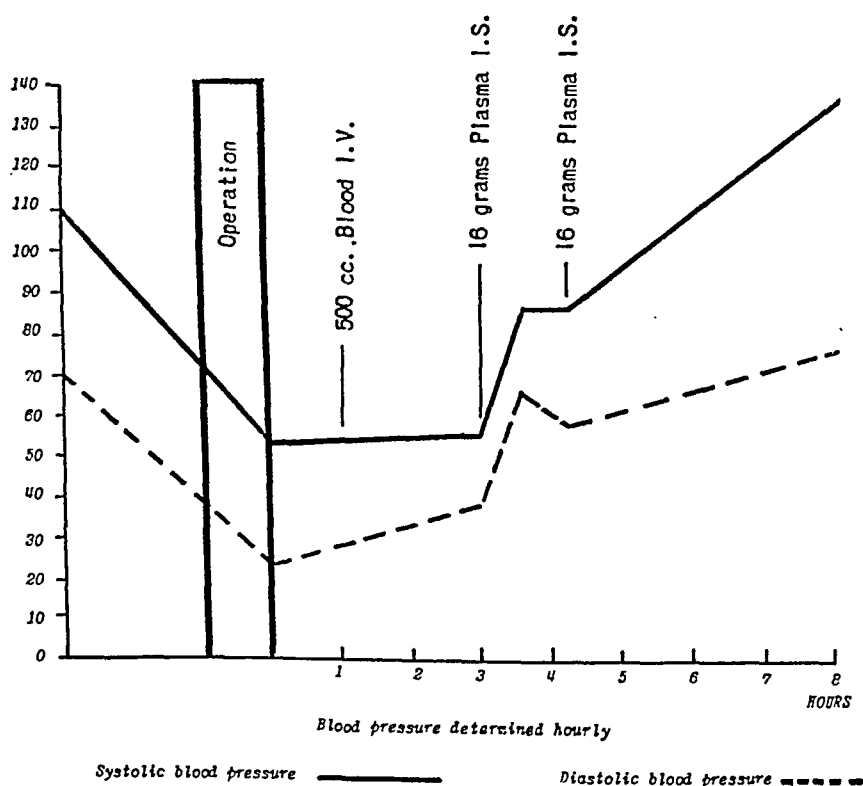
FIG. 3. Postoperative (esophagogastrostomy) changes in the systolic and diastolic blood pressure levels following administration (intrasternally) of *concentrated plasma* (16 grams in 50 c.c. distilled water). No other medication given during this period.

If animal plasma or albumin can ever be treated so as to be made nonantigenic,[46] or if human cadaver plasma or albumin becomes available commercially, most plasma banks will be eliminated. Commercial houses will readily take over such functions including the production of artificial antibodies,[43] which seems to be a distinct possibility in the future.

The Blood Transfusion-Plasma Unit dispenses many other intravenous fluids besides blood, plasma and serum, such as (1) amino acids for cases of malnutrition, hypoproteinemia, etc., (2) radioactive phosphorus, for cases of leukemia[44] and polycythemia,[45] (3) solutions of gelatin for cases of shock (if the pyrogenic substances in gelatin can be removed, it may become

a cheap and satisfactory agent in shock), (4) solutions of chlorophyll in cases of septicemia (the solutions used were ineffective in the cases of subacute bacterial endocarditis that we treated), (5) saline solutions containing alcohol and the vitamin B complex, (6) ascitic fluid, etc.; and also performs hemo-irradiation (Knott technic of irradiating auto-transfusions with ultraviolet light) of blood of patients when requested.

Conclusions

1. From 3,906 donors, blood was withdrawn at the Blood Transfusion-Plasma Unit of Jefferson Hospital during the year ending July 1, 1942. The Kahn or Wassermann tests were positive in 1.8 per cent of the donors.

2. The Blood Transfusion-Plasma Unit issued 2,869 blood transfusions, 3.2 per cent of which were followed by reactions, and 695 plasma (dried) infusions, 0.14 per cent of which were followed by reactions, during the year.

3. The reactions were classified as: (1) chills without fever; (2) chills with fever; (3) urticaria, and (4) incompatibilities. The pyrogenic reactions, or chills with fever, were most frequent.

Pyrogenic reactions, following transfusions arranged according to diagnosis and frequency of occurrence, follow:

Diagnosis	% of Reaction
a. Gynecological infections	12.2
b. Respiratory malignancies	8.4
c. Secondary anemias (secondary to leukemia or hemorrhages of the uterus or stomach, etc.)	6.3
d. Respiratory infections (bronchiectasis, lung abscesses,etc.)	5.5
e. Gastrointestinal infections (appendicitis, peritonitis, etc.)	5.1
f. Misc.	

By inference it is assumed that many of the pyrogenic reactions, following transfusions, were due to circulating foreign proteins (bacterial, fetal, nutrient, or cellular) in the recipient. However, since the percentage of reactions was much lower following plasma infusions in the same or similar cases, it must also be assumed that the red blood cells of a transfused blood are the agents that react with the circulating foreign proteins of the recipient. Measures to prevent transfusion reactions have been listed and it is hoped that the use of cellulose tubing, which is a very satisfactory substitute for rubber tubing in the administration of intravenous fluids, will reduce the number of pyrogenic reactions since such tubing is used but once.

4. Sturgis said [37] dried human plasma ultimately will be the agent universally used in shock. Dried human plasma apparently is as effective clinically as dried human albumin (when these agents are restored to one-fourth of their original fluid volume) and it is cheaper. Concentrated plasma almost invariably causes hemodilution and a rise in blood pressure (see figures 2 and 3). When plasma must be given in fox holes, on a rolling battleship or ambulance, or in civilian emergencies, long rubber tubes and

"drip" bottles can not be used conveniently. But 4 or 5 fold concentrated plasma, obtained by injecting, with the aid of a 50 c.c. syringe, 40 c.c. of distilled water into a vial containing 16 grams of plasma (the amount present in a pint of blood), can be administered intravenously or intrasternally within a very few minutes' time (see figure 1). The necessary equipment for the administration of concentrated plasma easily can be carried in a coat pocket and weighs only one pound. Concentrated plasma can be given to dehydrated patients without harm.[33] Ascites (in some cases of hypoalbuminemia due to nephritis and cirrhosis of liver) has been overcome by administrations of adequate amounts of concentrated plasma. Typing, crossmatching or skin testing is not necessary.

5. Intra-endothelial routes (intrasternal, etc.), other than venous routes of administering blood or plasma, have been life-saving in our experience.

6. Since Russia has administered successfully cadaver blood for transfusions for years it is suggested that the unlimited amounts of cadaver blood available in the nations' undertaking establishments be processed for plasma or albumin (preferably dried). Although it is the opinion of Ross T. McIntire,* Surgeon General of U. S. Navy, that there might be "strong public sentiment against the utilization of any product derived from cadavers . . .," the National Research Council † is giving the suggestion some consideration.

BIBLIOGRAPHY

1. A technical manual on the preservation and transfusion of whole human blood.
   A technical manual on citrated human blood. Both manuals can be procured from U. S. Office of Civilian Defense, Washington, D. C.
2. ROSENTHAL, N., WASSERMAN, L. R., ABEL, H., BASSEN, F., and VOGEL, P.: The organization of the blood bank at Mount Sinai Hospital, Jr. Mt. Sinai Hosp., 1941, viii, 210.
3. GREGORY, W. K., SHAPIRO, H. L., WEIDENREICH, F., and GREULICH, W. W.: Opposition to segregation of bloods from white and negro donors in blood banks, Jr. Am. Med. Assoc., 1942, cxix, 801.
4. Blood substitutes and blood transfusion. Edited by S. Mudd and Wm. Thalhimer, 1942, C. C. Thomas & Co., Springfield, Ill.
   (a) ROSENTHAL, N., and VOGEL, P.: Observations on blood transfusions from universal donors, page 297.
   (b) LEVINE, P., KATZIN, E. M., VOGEL, P., and BURNHAM, L.: The antigenicity of the Rh blood factor in transfusion and pregnancy—its role in the etiology of erythroblastosis fetalis, page 309.
   (c) JANEWAY, C. A.: Immunological and clinical studies on purified proteins of human and animal plasma, page 184.
   (d) HILL, J. M., and MUIRHEAD, E. E.: Desiccated plasma for national defense. Mass production methods based on the Adtevac process, page 78.
   (e) SCUDDER, JOHN: Electrophoretic patterns of serum and plasma, liquid and dried, page 126.
5. AUBERT, E. F., BOORMAN, K., DODD, B. E., and LOUTIT, J. F.: Universal donors with high titer isoagglutinins, effect of anti-A isoagglutinins on recipients of group A, Brit. Med. Jr., 1942, i, 659.

* Personal communication.
† Personal communication.

6. LEWISOHN, R., and ROSENTHAL, N.: Prevention of chills following transfusion of citrated blood, Jr. Am. Med. Assoc., 1933, c, 466.
7. HILL, J. M., and MUIRHEAD, E. E.: The advantages and clinical uses of desiccated plasma prepared by the Adtevac process, ANN. INT. MED., 1942, xvi, 286.
8. STRAIN, R. E.: Transfusion sites, Lancet, 1942, i, 61.
9. CRAVER, L. F.: Tenderness of sternum in leukemia, Am. Jr. Med. Sci., 1927, clxxiv, 799.
10. VOGEL, P., ERF, L. A., and ROSENTHAL, N.: Hematological observations on bone marrow obtained by sternal puncture, Am. Jr. Clin. Path., 1937, vii, 436–447 and 498–515.
11. HENNING, N.: Intrasternal transfusion as a substitute for the intravenous method, Deutsch. med. Wchnschr., 1940, lxvi, 737.
12. TOCANTINS, L. M., O'NEILL, J. F., and JONES, H. W.: Infusions of blood and other fluids via the bone marrow, Jr. Am. Med. Assoc., 1941, cxvii, 1229.
13. WIENER, A. S., and PENNELL, S. S.: The life-saving power of "safe" universal donor blood in exsanguinating hemorrhage, Am. Jr. Med. Sci., 1942, cciv, 1.
14. DeGOWIN, E. L., and HARDIN, R. C.: VI: Studies on preserved human blood: Reactions from transfusions, Jr. Am. Med. Assoc., 1940, cxv, 895.
15. KLENDSHOJ, N. C., McNEILL, C., SWANSON, P., and WITEBSKY, E.: Transfusion of conditioned universal blood, Arch. Int. Med., 1942, lxx, 1.
16. WOLFE, J. J., and DASGUPTA, C. E.: Acquired immunity to blood transfusion reaction: a new phenomenon, Brit. Med. Jr., 1941, ii, 807.
17. MASOR, N. A., GREENGARD, H., VOEGTLIN, W. L., SANDBLOM, J. P., and IVY, A. C.: Intercompatible reactions to blood transfusion related to the donor's diet, Federation Proceedings, Part 11, 1942, i, 59.
18. OEHLECHER, quoted by WIENER, A. S.: Blood groups and blood transfusion, 2nd Edition, 1939, C. C. Thomas, Springfield, Illinois.
19. KILDUFFE, R. A., and DeBAKEY, M.: The blood bank and the technique and therapeutics of transfusion, 1942, C. V. Mosby Co., St. Louis.
20. RIDDELL, V. H.: Blood transfusion, 1939, Oxford University Press, London.
21. WHITBY, L. E. H.: The hazards of transfusion, Lancet, 1942, i, 381.
22. PILLEMER, L.: The separation and concentration of the isohemagglutinins from human serums, Science, 1943, xcvii, 75.
23. BRAINARD, H. H.: Renal insufficiency following transfusion of compatible blood, Am. Jr. Obst. and Gyn., 1940, xl, 142.
24. MARRIOTT, H. L., and KEKWICK, A.: Volume and rate in blood transfusion for relief of anemia, Brit. Med. Jr., 1940, i, 1043.
25. SAZONTOV, V. I.: Transfusions of blood containing neither agglutinogens nor agglutinins, Vestnik khir., 1941, lxi, 15 (abst. Jr. Am. Med. Assoc., 1941, cxvii, 1397).
26. HARPER, S. B., OSTERBERG, A. E., PRIESTLEY, J. T., and SELDON, T. H.: Changes in serum protein and hemoconcentration in man following transfusion of a solution of dried blood plasma, Jr. Am. Med. Assoc., 1941, cxvi, 1760.
27. HILL, J. M., and MUIRHEAD, E. E.: The advantages and clinical uses of desiccated plasma prepared by the Adtevac process, ANN. INT. MED., 1942, xvi, 286.
28. HILL, J. M., MUIRHEAD, E. E., ASHWORTH, C. T., and TIGERTT, W. D.: The use of desiccated plasma with particular reference to shock, Jr. Am. Med. Assoc., 1941, cxvi, 395.
29. COHN, E. J.: Properties and functions of the plasma proteins with a consideration of methods for their separation and purification, Chem. Rev., 1941, xxviii, 395.
30. BROWN, H. A., and MOLLISON, P. L.: A note on the transfusion of reconstituted dried human serum, Brit. Med. Jr., 1940, ii, 821.
31. ROSE, B., WEIL, P. G., and BROWNE, J. A.: On use of concentrated pooled human serum and pooled lyophile serum in treatment of shock, Canad. Med. Assoc. Jr., 1941, xliv, 442.
32. Editorial, Protein deficiency, Jr. Am. Med. Assoc., 1942, cxx, 455.
33. HEYL, J. T., and JANEWAY, C. A.: The use of human albumin in military medicine, U. S. Naval Med. Bull., 1942, xl, 785.

34. WOODRUFF, L. M., and GIBSON, S. T.: The clinical evaluation of human albumin, U. S. Naval Med. Bull., 1942, xl, 791.
35. COGHILL, R. D., FELL, N., CREIGHTON, M., and BROWN, G.: Elimination of horse-serum specificity from antitoxins, Jr. Immunol., 1940, xxxix, 207.
36. NEURATH, H., ERICKSON, J. O., and COOPER, G. R.: The antigenic properties of native and regenerated horse serum albumin, Science, 1942, xcvi, 116.
37. STURGIS, C. C.: National Research Council Bulletin on Shock, 1940.
38. THALHIMER, W.: Intravenous injection of pooled normal plasma or serum, Jr. Am. Med. Assoc., 1942, cxx, 1263.
39. AUBERT, E. F., BOORMAN, K. E., and DODD, B..E.: The agglutinin-inhibiting substance in human serum, Jr. Path. and Bact., 1942, liv, 89.
40. WHITE, C. S., COLLINS, J. L., and WEINSTEIN, J. J.: The treatment of surgical and traumatic shock with a citrated plasma-saline mixture, Am. Jr. Surg., 1941, liv, 701.
41. HEATH, F. K., and PROVINCE, W. D.: Preservation of human plasma; report of studies with sulfonamide compounds, Jr. Am. Med. Assoc., 1942, cxviii, 1034.
42. JONES, H. W., TOCANTINS, L. M., ERF, L. A., and MUNRO, F.: Concentrated blood plasma intrasternally in the treatment of shock, Trans. Assoc. Am. Phys., 1942, lvii, 88.
43. PAULING, L., and CAMPBELL, D. H.: The production of antibodies in vitro, Science, 1942, xcv, 440.
44. ERF, L. A., TUTTLE, L. A., and LAWRENCE, J. H.: Clinical studies with the aid of radio-phosphorus. Therapeutic effect on patients with leukemia, ANN. INT. MED., 1941, xv, 487.
45. ERF, L. A., and JONES, H. W.: Radio-phosphorus—an agent for the satisfactory treatment of polycythemia, and its associated manifestations, ANN. INT. MED. In press.
46. Editorial: Possible substitutes for human plasma, ANN. INT. MED., 1943, xviii, 251.
47. POST, J., and PATEK, A. J.: Serum proteins in cirrhosis of the liver, Arch. Int. Med., 1942, lxix, 67.

CHRONIC SEASICKNESS *

By ROBERT S. SCHWAB, Lieutenant Commander, MC, USNR,
Chelsea, Massachusetts

THE history of seasickness is as old as that of any disease. The Romans and Greeks mention it in several of their writings, and notables such as Cicero and Caesar suffered frequently from this condition. Nelson, although he spent most of his life at sea, was a victim of seasickness most of the time. An interesting early description of large numbers of men being sick is found in a diary of Dr. Isaac Senter [1] who was a medical officer attached to the ill-fated expedition under General Benedict Arnold which
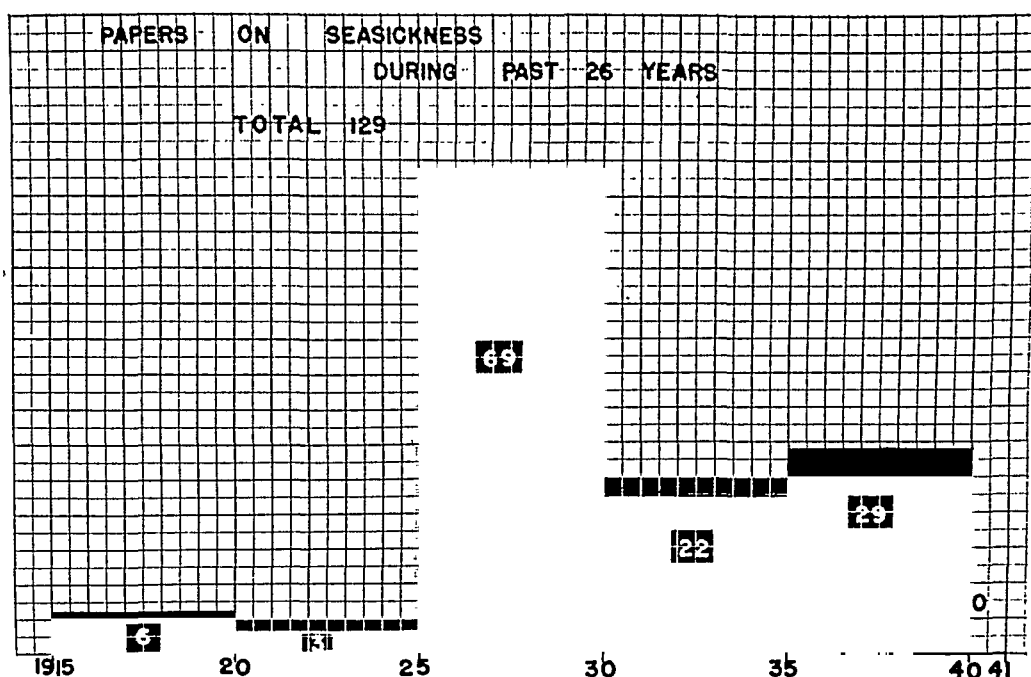
FIG. 1. A graph showing the distribution of literature on the subject of seasickness during the last 25 years.

in 1775 attempted to capture Quebec. This expedition of some 1500 men sailed in small ships from Newburyport to the mouth of the Kennebec River in Maine. Over 90 per cent of the soldiers were very seasick during the entire trip and it was noted that they considered themselves fortunate on landing at the Kennebec that they did not have an enemy to fight.

There is a very extensive literature on the subject. It is interesting that during the lean years associated with wars and depressions in the past, little attention has been focused on this subject by the medical profession. Only nine papers were published, for example, from 1914 through 1920. In prosperous years when people travelled extensively, such as the years from 1925 to 1930, over 69 articles on this subject were published. Since 1935 there has been a marked falling off of publications in relation to this subject (figure 2). In the last 25 years over 140 articles on seasickness have ap-
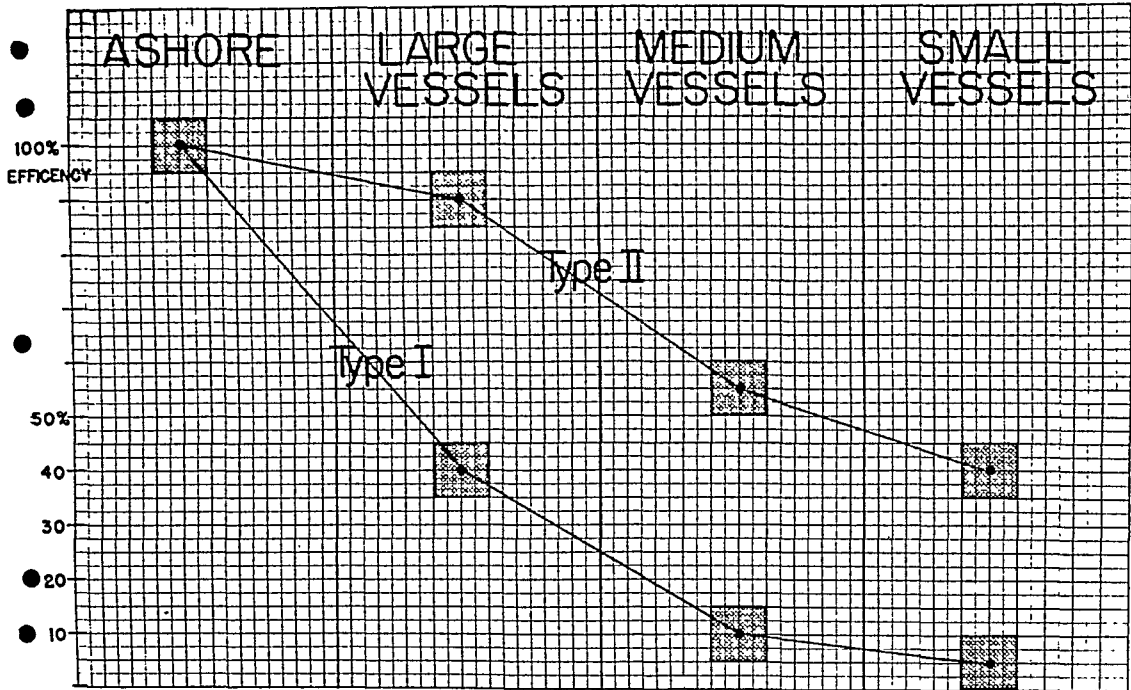
FIG. 2. Comparison of the efficiency of Type I seasickness and Type II seasickness on different size vessels.

peared in the various medical journals in the world.[2] The author has the complete bibliography of these articles in his preliminary paper of October 1942. Some of these are merely reports and personal theories by the medical officers of ships or articles written by doctors who have travelled. A few are worth reading, and a few more include careful clinical and some laboratory studies.

The general feeling is that seasickness is a complicated affair with many causes and a very complicated etiology. It is generally agreed that susceptible individuals have some hypersensitivity of the vegetative nervous system. There are those in the literature who advocate the theory that this trouble is concerned entirely with the vestibular system. Equally convincing data involve the psyche and there is evidence that the visual, olfactory and proprioceptive systems are also concerned. The wisest view is that various

types of stimuli set off the syndrome (table 2) and that different conditions in different individuals modify the general picture.

TABLE I

The order in which symptoms usually appear in seasickness.

1. Anorexia {Tobacco / Food
2. Loss of interest
   Seclusiveness
3. Salivation
   Sweating
4. Vertigo
   Nausea   Headache
5. Vomiting

TABLE II

Six sources of stimuli which contribute to the development of seasickness in a subject.

A. Psychic
B. Olfactory
C. Visual
D. Vestibular
E. Gastrointestinal
F. Proprioceptive

The treatment of this disease has varied throughout the pharmacopeia with a general agreement that sedative drugs and atropine and related drugs show the most promise.   One homeopathic physician, a French medical officer on a liner, believed that since seasickness was the result of a human being being thrown about on the salty ocean the natural remedy would be the ingestion of sea water which would be thrown about in his stomach.   I might add the results were very discouraging to him.   About three-quarters of the references to seasickness include the adage that the only sure cure is to sit under a live oak tree.

The subject as concerns the United States Navy was first brought to my attention when I came to active duty at the Naval Hospital in December 1941.   Here I found to my surprise that four or five patients on the Neuro-Psychiatric Ward had been sent in because of seasickness.   During the last fourteen months I have had the privilege of examining over 115 naval personnel who suffered with chronic seasickness, severe enough to bring them to the hospital either as out-patients or as ward patients.

We have found that this group is divided roughly into two main divisions, the first of which I shall call Type I.   It is composed of people who get sick, not only at sea but on trains, busses, cars, elevators, swings and roller coasters, and who suffer from a variety of other motion sicknesses.   These people when they get to sea become very seasick and stay sick.   Their efficiency is low, they lose considerable weight and they are more or less useless on the vessel.

A second group of individuals suffers from seasickness particularly during rough weather.   We call them Type II.   They have no history of motion

sickness. They are able to do their work with reduced efficiency but are rarely laid up and have little weight loss. They are usually valuable men on their vessels. These two groups at first seemed quite distinct but as the number of cases became larger, it was seen that there might be an intermediate number which I have arbitrarily called Type-IA. This group gives a history of some motion sickness but gets along reasonably well in quiet water or on a big ship. Weight loss is small and efficiency is greater than in the original Type I.

We found to our surprise that 50 per cent of the subjects suffering from chronic seasickness showed abnormalities in the gastrointestinal tract. These were first picked up by barium fluoroscopy done through the coöperation of the Naval Hospital roentgenologist, Lieutenant Commander H. D. Goehring, who fortunately has had special training and experience in mucosal relief studies of the gastrointestinal tract. He found that in a man recently returned from five or six weeks of seasickness at sea, one could demonstrate the following: (1) Marked irritability of the pylorus and duodenum with resulting pyloric spasm. (2) Marked increase in gastric secretion even with fasting. (3) Some increase in the gastric rugae. (4) Loss of peristalsis. These findings persisted in some of our patients for three or four weeks, gradually becoming less marked and in one patient nearly disappearing after

TABLE III

Some of the more common diagnoses under which seasickness appears on entry into a naval hospital.

1. Psychoneurosis
2. Gastric neurosis
3. Gastric ulcer
4. Gastritis
5. Headache
6. Sinus trouble
7. Deviated septum
8. Appendicitis
9. Back strain
10. Syncope

three months.[3] In 15 of our cases we have checked the barium findings with gastroscopic examination through the coöperation of Dr. Edward Benedict of the Massachusetts General Hospital. He has found, in this group, evidence of mild, chronic superficial gastritis. The significance of these findings is not absolutely clear to us at this time, but they do show that this disease has its pathologic lesions like any other condition met in medicine, and it behooves us to study further the causes and the treatment for this condition.

Another feature of seasickness is the many diagnoses which mask the actual incidence of this state. The reason for this is clear if one remembers that being seasick is considered by most of us as something of a weakness, and by some as a disgrace. Therefore, medical officers and pharmacist's mates out of kindness or other motive will give to the seasick sailor one of the diagnoses seen in table 3. We have seen one or two patients whose sea-

sickness was severe enough to cause abdominal pain which persisted and which resulted in their being sent to a hospital and operated on for appendicitis, thus creating in my mind the syndrome of the seasick appendix.

A most interesting complication in this group is a psychoneurosis. This warrants a more detailed study. We have found, for example, that 74 per cent of the Type I individuals show neurotic trends of one sort or another, such as an easily upset stomach, a tendency to nausea and vomiting from unpleasant sights, a labile vegetative system so that syncope is common, a history of odd dizzy attacks and so forth. A number of these people, however, go through their early life without any serious psychiatric complication or illness in spite of these trends. One could say very definitely that they were vulnerable individuals with this history of being made sick in a variety of ways when exposed to motion. In the past, however, their difficulty has been taken care of by the simple method of avoiding or leaving the conveyance which made them ill. They enter the Navy, impelled to join by natural patriotic emotion, get along reasonably well at the training station, and find themselves assigned to a small ship such as a destroyer or a mine sweeper. If this happens to occur in the North Atlantic in the fall, winter or spring when it is rough, they experience seasickness the first time the vessel leaves the wharf. Now they are unable to leave the source of their disturbance, sometimes for as long as three weeks, and individuals of this type lie in their bunks vomiting, losing weight, and being very, very miserable. They are sometimes criticized or teased by their fellow sailors or officers for not overcoming this disability by will power. At any rate, they feel discouraged and inadequate, and the uselessness of their life on the ship is very obvious to them. When they finally are sent into the hospital because of the failure of the condition to disappear, whether it is under the diagnosis of gastric ulcer or frank seasickness, they now have developed definite psychoneurosis. The very thought of returning to that ship or to sea duty in general causes a host of conditioned reflexes to appear. These individuals, in an effort to prevent their return to life at sea, usually do one of three things:

1. A few with lowered appreciation of the seriousness of their offense run away.

2. A large number develop chronic complaints in the hospital not related to seasickness, such as backache, headache, stomach ache, anorexia and apprehensions of all sorts. These symptoms increase in intensity and frequency as the day of return to duty approaches. These symptoms are real and disturb the patient's equilibrium even when he is on leave. We have observed such subjects who were unable to make the usual adjustment when they went home, being sick at the family table, unable to sleep, and a few cases of psychic impotence have been brought to my attention which never existed previously.

3. The third group, small in number, simply break down in a fear reaction, sometimes tearful, sometimes belligerent, and say they cannot under

any circumstances return to sea. They plead a shore job, a transfer to the army.

We have tried recommending larger vessels, and even shore duty, for many of these individuals when they were sent back to duty, but the threat and possibility of being sent back to sea on a smaller ship is ever present and the neurotic symptoms persist. Sooner or later these individuals are sent back to the hospital and in our experience have to be surveyed out of the Navy.

Example 1. A 21 year old farmer from one of the middle western states joined the Navy in May 1942. He had never been on a ship of any description before in his life. He gave a history of being sick in automobiles, trains, busses, swings and roller coasters. He would vomit or feel nauseated by unpleasant smells or sights. There was a history of "nervous stomach" in his family. He himself had no previous gastrointestinal trouble except that induced by motion. He had gone through high school and had not had any obvious psychiatric disturbance. After high school he obtained a job on a farm and began to have occasional headaches when he worked too hard. Several times during one year he had mild dizzy spells and fainted twice from emotional disturbances. He was very upset over a love affair going wrong, after which he had nothing to do with girls and was seclusive for nearly a year. After joining the Navy he did well at the training station and was assigned to a destroyer. He became seasick as soon as the vessel left the wharf, being overcome with dizziness and vomiting so that he had to lie in his bunk. During the entire trip of 11 days he was unable to get on his feet and lost 13 pounds. Several times during the last three days of the trip the medical officer noted that he cried when interviewed and was very discouraged and unhappy. The ship made two more trips with the patient with the same results. At the end of the third trip the patient noted some blood-stained vomitus and became conscious of a pain in his stomach. There was marked exaggeration of his symptoms, and as a result of this he was sent to the hospital with a diagnosis of acute gastritis. After a fortnight's stay in the hospital with study on the wards, he was given 10 days leave. He found when he got home that he was very nervous, and he had disturbing dreams of being seasick in rough weather so that sleep was difficult. On three occasions he vomited at the family table, something that he had never done before. He had no inclination to meet his old friends and remained indoors most of the time during his leave. He reported that he cried most of the night before leaving for his station. When the decision was being made in regard to his disposal he developed pain in his back and a limp which was obviously hysterical. These all disappeared and his condition improved considerably when he was finally told that he would be surveyed out of the service and sent home.

The patients suffering from marked constitutional susceptibility to motion sickness, i.e., Type I, who do not show the neurotic symptoms mentioned above and who seem like valuable men to the service such as a doctor or radio engineer, signal man, etc., after a medical survey have been recommended for shore positions and have done well, of course, when they were thus assigned.

Example 2. A radio mechanic coming from the eastern seaboard graduated from high school and joined the Navy in 1940. He gave a history of susceptibility to motion sickness such as cars, trains, busses, swings, etc. There was no history of a neurosis in this case at any time in his past. His first six months in the Navy were

on shore. There was a brief trip on a transport lasting two weeks during which time he was sick eight days. He then was sent to a special school for three months and assigned to a destroyer where he was sick approximately 80 per cent of the time. He was, however, able to stand most of his watches in spite of his seasickness, although he lost a good deal of weight and his efficiency was considerably reduced. He was keenly interested in remaining in the service if he could avoid the difficulty of a small boat existence. In the hospital he was an obviously normal person of considerable value to the service. He was finally assigned to a shore position and is doing very well in this capacity.

TABLE IV

The two types of chronic seasickness compared as to the presence of motion sickness and efficiency

	Type I	Type II
Number of cases	51	55
Motion sickness	Yes	No
Efficiency	0–20	40–60
Weight loss	Marked	Slight
Disposal	(Shore or Discharge)	(Larger Ship and Treatment)

TABLE V

Clinical findings in the two types of seasickness compared. Note the exceedingly high percentage of neurotic individuals in Type I

	Type I	Type II
Number of cases	51	55
Neurotic	74%	24%
Fainters—dizzy spells	57%	14%
Gastrointestinal history	72%	8%
No neurotic G.I. or syncope history	17%	65%
Abnormal G.I. series	60%	30%
Abnormal gastroscope	30%	10%

These individuals who do not develop psychoneurosis and whose recovery from seasickness is rapid often can be sent back to sea on a larger ship or greatly helped by one of the usual drugs. I have had follow-up reports on eight subjects who have readjusted by the development of tolerance to sea duty. Three of these have remained on the same ship, i.e., destroyers; five have been transferred to larger vessels with a reduction in their trouble.

Example 3. A 27 year old salesman with no history of motion sickness and no history of neurosis joined the Navy in June 1942. He spent two months on a cargo vessel, being sick only two days out of 60. Following this he was transferred to a small patrol craft operating in coastal waters. He was sick approximately five out of seven days and felt that he was not doing his work although he was able to stand all his watches. Some slight blood-stained vomitus brought him to the hospital. It was recommended that he be assigned to a larger ship which fortunately was available. Six months later he reported by letter that he had not suffered from seasickness and was doing his work without any trouble.

The subject of efficiency of men suffering from seasickness deserves something in passing. It is obvious that a man with marked nausea, vertigo, headache, vomiting and a certain amount of apprehension and discouragement from the condition accompanying the above, is not as able a man as his

unaffected fellow.   This difference in ability is not easy to measure but it involves alertness, skill, temper, resistance to infection, cold, heat, immersion and so forth.   A small vessel with a crew of 100 men which has 50 of them violently seasick is not as efficient as a vessel with 100 men not affected. Therefore, this condition is not to be laughed at or disregarded, and has a very definite military bearing.   We feel that the wisest way to handle the situation is to try to keep out of the service those individuals suffering from chronic motion sickness in the past, and these can be picked up by a questionnaire.   Those that are found in the service should be sent to shore jobs if their abilities warrant their retention in the service.   This is particularly true of a man who has had considerable expensive training before this condition is noted.   Others not suffering from motion sickness can usually develop tolerance and can be helped by some of the anti-seasick remedies.

BIBLIOGRAPHY

1. SENTER, DR. ISAAC: The Journal of Isaac Senter, Philadelphia. Published by the Historical Society of Pennsylvania, 1846.
2. SCHWAB, ROBERT S.: Chronic seasickness. Neurological, psychiatric, and Naval aspects, U. S. Naval Med. Bull., 1942, xl.
3. GOEHRING, H. D.: Roentgenological findings in seasickness. To be published.

OCCLUSIONS OF THE ABDOMINAL AORTA: A STUDY OF 16 CASES OF SADDLE EMBOLUS AND THROMBOSIS *

By NATHANIEL E. REICH, M.D., *Brooklyn, New York*

A HIGHLY dramatic episode in medicine is a condition variously described as thrombosis or embolism of the abdominal aorta and "rider's" or "saddle" thrombus or embolism. Approximately 150 cases of obstruction of the abdominal aorta have been reported in the literature to date. In the main, these have consisted of scattered reports of from one to five cases. We have been fortunate in accumulating 16 cases over a period of five years at Kings County Hospital. Eleven of these were autopsied and two recovered by recanalization. As far as is known this is the largest group to be studied. A careful survey of these cases reveals certain facts in the etiology, age-sex distribution, diagnosis and treatment. An analysis of the causes of failure in early diagnosis is also considered.

CASE REPORTS

Case 1. F. O., white female, aged 32, was admitted with a history of sudden loss of speech of six months' duration. She had had scarlet fever at the age of nine. At 21 she developed dyspnea and palpitation and a diagnosis of mitral stenosis was made. Two years prior to admission the patient had to be digitalized because of acute cardiac failure with pulmonary edema but fibrillation continued. While at work six months previously she fell and remained unconscious for a period of 10 days, with loss of voice and right hemiplegia. Two weeks before her present admission she awoke and coughed up a large amount of blood which was attributed to pulmonary infarction.

Examination revealed marked emotional instability with aphasia. There was cardiac enlargement with a double murmur at the apex. The second pulmonic sound was accentuated and there was auricular fibrillation with occasional extrasystoles. Blood pressure was 175 mm. Hg systolic and 95 mm. diastolic. The residual right hemiplegia was attributed to embolization to the left middle cerebral artery secondary to rheumatic heart disease. Two weeks following admission she developed dyspnea with a crampy pain in the left leg which was thought due to another embolus. Seventeen days after this episode she complained of epigastric pain and had tenderness in the left upper quadrant which was thought to be the result of a splenic embolism. Three weeks later she complained of nausea, vomited 5 c.c. of dark red blood, and had slight epigastric rigidity. Two and a half months later she vomited and complained of abdominal cramps. A tender area with rigidity was noted in the right upper quadrant which was interpreted as caused by acute cholecystitis or a penetrating peptic ulcer. Medical consultants suggested either acute appendicitis or small mesenteric thrombosis. Surgical intervention was not considered feasible at any time because the patient was an extremely poor operative risk. Later that day she complained of precordial pain, vomited, became extremely weak, and finally died.

Laboratory examinations included a roentgenogram of the heart which revealed a prominent pulmonic conus compatible with an underlying congenital heart lesion. Electrocardiographic study showed no axis deviation and only slight myocardial impairment. Wassermann reaction and blood cultures were negative. Terminally the blood urea rose to 135 mg. and the sugar was 84 mg. per 100 c.c. of blood. The temperature was never over 100.5° F. throughout her two year hospital stay. The urine presented clumped leukocytes and traces of albumin but no red cells terminally.

Autopsy revealed a heart weighing 210 grams; the left auricle was markedly dilated, whereas the left ventricular cavity was small, and the wall measured 1 cm. in thickness. There was a marked thickening and fusion of the mitral valve with stenosis and insufficiency. It was free of old or recent vegetations. There were no thrombi present. The intima of the aorta was bright yellow and smooth. Just below the opening of the celiac axis extending down to the external iliac arteries, the lumen of the aorta was completely occluded by a firm, red-gray, friable thrombus. This mass extended down into the smallest branches of the superior and inferior mesenteric and splenic arteries. The mass was adherent throughout to the arterial walls and varied considerably in shade from place to place. Infarctions of the proximal two-thirds of the large intestine and the entire small intestine caused them to appear dark red and lusterless. In addition, there were large infarctions of the kidneys, spleen and in the left hemisphere of the brain extending from the ependyma of the left ventricle to the tip of the occipital lobe. The latter was cystic and orange-yellow. Microscopic studies revealed the lumen of the aorta to be occupied by a large antemortem thrombus with early canalization and basal organization. There was an infiltration of lymphocytes and histiocytes with edema between the adventitia and media. The large arterial branches were similarly involved. Other gross pathological changes were corroborated by extensive microscopic studies. The final diagnosis was inactive rheumatic heart disease with mitral stenosis and insufficiency, with embolization to the abdominal aorta, and thrombosis of the mesenteric, iliac, splenic and renal arteries.

Comment. The age, cardiac history, rheumatic heart disease with fibrillation, normal aorta, multiple embolization for two years (brain, kidneys, spleen, superior mesenteric artery and extremities) were completely in harmony with the diagnosis of an aortic occlusion due to embolization. This interesting case was carefully followed for two years. It was remarkable to note that although the acute symptoms dated back 11 days before death and produced various clinical pictures of acute cholecystitis, acute appendicitis, peptic ulcer and mesenteric thrombosis, the extremities remained uninvolved and findings were localized to the abdomen only. Hence, although the diagnosis was not made, mesenteric thrombosis was correctly suggested. Terminally, the thrombotic process progressed rapidly on the embolic nidus.

Case 2. E. M., white, married, Puerto Rican female, aged 34, was admitted with sudden onset of excruciating pains in both legs with inability to walk, numbness and coldness of both feet. After an hour she developed sharp knife-like pains in both calves and was unable to move either leg. They felt cold and numb and the pain became dull and aching. The following day she requested hospital treatment. Her past history revealed attacks of dizziness, dyspnea, palpitation and edema. She had had intermittent attacks of joint pains involving chiefly the right leg and knee over a 10 year period.

Physical examination revealed an enlarged heart with harsh presystolic and systolic apical murmurs and a systolic apical thrill. Blood pressure was 150 mm. Hg systolic and 70 mm. diastolic. There was no enlargement of the liver or spleen.

Aortic pulsations were felt to a level just below the umbilicus. No pulsations were palpated in the femoral, iliac, popliteal and dorsalis pedis arteries. The right leg was more involved than the left and was cold, clammy, blue and dry. Although the sensation of touch was decreased, pressure and pain were exaggerated. The calves were edematous, swollen and firm. A diagnosis of enlarged heart due to rheumatic heart disease, mitral stenosis and insufficiency, ventricular extrasystoles, class II A, was made. In addition, a diagnosis was made of a rider's embolus possibly due to a subacute bacterial endocarditis. The condition progressed steadily until bilateral mid-thigh lines of demarcation formed. It was of interest to note the clear outlines of the capillaries on the plantar surfaces with mummification by dry gangrene. Treatment consisted of large doses of papaverine, dry heat and an oscillating bed, since surgical intervention was not advisable. The temperature ranged between 99 and 103° F. The patient gradually became worse and finally died 17 days later.

Laboratory Studies. The electrocardiograph showed auricular hypertrophy, right axis deviation and myocardial damage. A bedside roentgenogram revealed an enlargement to the left and enlargement of the left auricle due to rheumatic heart disease. Two blood Wassermann reactions were negative. Three blood cultures taken for *Streptococcus viridans* were negative. The leukocyte count was 10,000 with 94 per cent polynuclears.

Autopsy revealed both lower extremities to be reddish black, swollen and gangrenous with many vesicles containing clear fluid. The heart weighed 360 grams and presented rheumatic endocarditis with stenosis of the mitral, aortic and tricuspid valves. Pearly-gray excrescences were present over the thickened valve edges. Many small and large round and odd shaped vegetations were found over the auricular surfaces. One of these vegetations occluded the ostium of a Thebesian vessel. The aorta and large branches appeared thin-walled and elastic throughout. At the level of the fifth lumbar vertebra, the lumen of the aorta was occluded by a soft, grayish-red thrombus that was firmly attached to the intima and extended beyond the bifurcation of the femoral arteries. A branch of the pulmonary artery supplying the right middle lobe was occluded by a soft, adherent antemortem thrombus with pulmonary infarctions. On microscopy, the intima of the aorta consisted of many layers of hyalinized connective tissue. The media was replaced by a considerable amount of dense connective tissue. The adventitia and vasa vasorum were not unusual. In the sections exhibiting the thrombus there were masses of red blood cells, polynuclears and proliferating fibroblasts enmeshed in fibrin. Sections of the auricle showed similar areas of attached thrombi with infiltrating fibroblasts and small mononuclear cells. The adjacent muscle cells were necrotic.

The final diagnosis was rheumatic endocarditis with stenosis of the mitral, aortic and tricuspid valves with marked hypertrophy and dilatation of the heart. Secondary embolization from the heart to the abdominal aorta with succeeding thrombus proliferation resulted.

Comment. Embolization from the left auricle was the cause of aortic obstruction in this case. The age, rheumatic history, cardiac findings, acute onset of pulmonary infarction and elastic aorta and branches were all in its favor. Embolectomy was the treatment of choice but the patient sought relief two days after the onset. The immediate use of a constantly oscillating bed, papaverine and dry heat undoubtedly prolonged her life for two weeks despite the severity of the occlusive process.

Case 3. J. H. (case of Dr. B. A. Fedde), white male, janitor, aged 50, was admitted with pain in the epigastrium and the lower right quadrant. He had had malaria 36 years previously and had been operated on for chronic appendicitis one

year earlier. Thirty years previously he had been crushed by a car in a coal mine, the maximum impact being at the umbilicus. He had had three attacks of gonorrhea and drank heavily until two years prior to admission. He was unable to walk more than three blocks without getting severe cramps in both legs requiring rest for several minutes before continuing. His feet were generally cold.

Examination revealed a poorly nourished male. The heart apex was in the sixth interspace in the midclavicular line. No murmurs or irregularities were heard. Blood pressure was 130 mm. Hg systolic and 90 mm. diastolic. There was a hernia at the site of the previous operation as well as a right femoral hernia. The brachial artery was tortuous and sclerotic and the dorsalis pedis and posterior tibial artery pulsations could not be palpated. Because of abdominal and loin pain, a right ureteral calculus was considered. Pyelography revealed a mobile right kidney with slight hydronephrosis due to uretero-pelvic kinking. Right ureterolysis and nephropexy were performed. The immediate postoperative condition was good. However, the following day he complained of pain in both legs followed shortly by a mottled, purple discoloration. Although both legs were fairly warm at first, pulsations were not felt in the femoral, popliteal or tibial arteries bilaterally. The reflexes were lost and the extremities became cold in an hour and a half, more markedly on the right. A diagnosis was made of a postoperative saddle thrombus. Surgery was deemed futile and the patient died the same day. The temperature course was normal throughout.

Laboratory. Roentgenographic studies revealed a normal gall-bladder and gastrointestinal tract. Calcification of the iliac vessels was noted. There was no free acid and 23 to 45 points of total acidity on gastric analysis. Blood chemical tests, Wassermann reaction, three urinalyses and urine culture were negative.

Autopsy revealed the recent loin incision and nephropexy which were uninfected. The heart weighed 360 grams. The left ventricle measured 1.4 cm. in thickness. The valves and endocardium were free of vegetations or thrombi. The intima of the aortic arch presented numerous non-ulcerating atheromatous calcified plaques. A large thrombus was found completely occluding the aorta from the renal arteries to its bifurcation. The thrombus was firm, friable, dark red and firmly adherent to the intimal surface. Just below the upper end of the thrombus was a ring of calcified hard atheromatous degeneration which was ulcerated but there was no point of rupture of the aorta. The thrombus extended into the iliac arteries and their branches. The right iliac vessel was dark blue, having undergone a marked degree of atheromatous degeneration. There was no evidence of renal infarction and the right renal artery was free of sclerosis. On the left side, the artery consisted of a section of thin, fibrous tissue interposed between two stumps of normal artery. There was an aberrant vessel arising 0.5 cm. above the site of the normal renal artery which entered the lower pole of the left kidney after crossing the normal artery. This vessel was slightly narrowed at the point of crossing but contained no thrombus.

Comment. An evaluation of the factors involved in this case is somewhat complex. Undoubtedly the primary factor concerned with the production of the aortic occlusion was the ulcerated ring of calcified atheromatous degeneration near the renal arteries, most marked just below the upper end of the thrombus. The marked calcification of other blood vessels strengthens this belief. What additional influence, if any, the aberrant renal artery played is difficult to ascertain since there was no thrombosis or sclerosis of the renal vessels beyond the occlusion at the mouths of these vessels. Probably this congenital defect played a very small rôle. Although trauma is an accepted cause for thrombosis, certainly the crushing impact at the umbilicus could not have been expected to exert any influence after 30

years. It is conceivable that traction at the time of nephropexy, however, may have contributed some measure of trauma at the site of the ulcerated ring. The precipitating factor producing a thrombus at this site was the increase in platelets and fibrinogen which follow any operation. In addition, there was an initial drop in blood pressure during operation with a slowed blood stream which aided clot formation. Hemoconcentration also occurred from loss of fluids and blood, as well as vomiting, diuresis and acidosis. The importance of this factor arises from the physical fact that the velocity of a fluid in a tube is inversely proportional to its viscosity and directly proportional to the driving pressure to which it is subjected. The fact that thrombosis may occur in different blood systems of the body (e.g., pulmonary artery and portal vein as in case E. M.) also speaks strongly for the influence of these factors. This has been noted elsewhere.[1]

Case 4. R. H. (case of Dr. G. A. Merrill), white housewife, aged 62, was admitted with a stroke of six hours' duration. She had had a heart attack of an unknown type six months previously, and had been given digitalis until one month before admission.

Examination revealed a well developed female with a complete right hemiplegia and aphasia. The heart was slightly enlarged and rhythm was regular. Blood pressure was 160 mm. Hg systolic and 110 mm. diastolic. There were a few basal rales. The diagnosis was arteriosclerotic heart disease with thrombosis of the left middle cerebral artery. Except for urinary incontinence she progressed fairly satisfactorily. Eleven months later she suddenly become comatose with left hemiplegia and died two days later.

Laboratory studies included an electrocardiogram which presented left axis deviation and severe myocardial damage. Blood chemical tests and Wassermann reaction were normal. The temperature was normal throughout.

Autopsy examination of the brain revealed a fresh thrombus of the right middle cerebral artery. The heart weighed 425 grams and revealed moderate coronary sclerosis and myocardial fibrosis. The aorta presented a marked atherosclerosis with a saddle thrombus at the bifurcation of the aorta extending into both common iliac and right internal iliac arteries with complete occlusion. The entire length of the thrombus was 10 cm. There were large ulcerated plaques at the bifurcation of the aorta. In addition, there were an acute hemorrhagic cystitis, gastric polyp and generalized arteriosclerosis.

Comment. Undoubtedly, the age, generalized arteriosclerosis, regular sinus rhythm without mural thrombi, old and recent thrombotic occlusions of the cerebral vessels, marked atherosclerosis of the aorta with large ulcerated plaques at the bifurcation are all in favor of a thrombo-arteriosclerotic process. The unusual feature of this case is that although she was acutely ill for two days she presented no symptoms or signs of aortic thrombosis. The conclusion one may safely draw is that the extensive thrombosis developed rapidly just prior to death.

Case 5. E. B., white unemployed male, aged 80, was admitted with cellulitis of the lower extremities and dyspnea. He had been troubled with asthmatic bronchitis and expectoration for a half year but was in excellent health previously.

Examination revealed occasional coarse moist rales, especially at the bases, and rhonchi throughout. The heart sounds were regular but of poor quality and no mur-

murs were present. Blood pressure was 140 mm. systolic and 70 mm. diastolic. A diagnosis of bronchiectasis with secondary emphysema was made. He became increasingly weaker with terminal fibrillation and died one and a half years after admission.

Laboratory examinations included an electrocardiographic study presenting evidence of myocardial fibrosis. Roentgen-ray revealed no pulmonary disease. Blood Wassermann reaction was negative. The temperature never was above 100.5° F.

Autopsy revealed bronchiectasis of both lower lobes with terminal bronchopneumonia. The heart weighed 280 grams and showed evidence of myocardial fibrosis. The arch and ascending aorta were moderately dilated with many sclerotic plaques. The thoracic and abdominal aorta had many small sclerosed plaques some of which were calcified and ulcerated. There was a large thrombus occluding the abdominal aorta for a distance of 5 cm. above the bifurcation. On section, the thrombus contained a large area filled with soft red necrotic material. The thrombus did not extend into the left common iliac artery, but in the right common iliac artery there was a small red-gray thrombus which partially occluded the lumen. The external appearance of the body was negative. The final diagnosis was atherosclerosis with ulceration and thrombosis of the abdominal aorta and the right common iliac artery.

Comment. This occlusion was due to thrombo-arteriosclerosis of the aorta. As in the preceding case, there was no subjective or objective evidence to suggest thrombosis of the abdominal aorta even just prior to death.

Case 6. A. D., white female, aged 38, previously in fair health, suddenly lost consciousness the night before admission. During childhood she suffered from "growing pains" and recently developed shortness of breath. Two years before she was told she had heart disease.

Examination revealed an obese female with dyspnea and cyanosis. The heart was slightly enlarged to the left with a double apical murmur and auricular fibrillation. Blood pressure was 120 mm. Hg systolic and 80 mm. diastolic. There was a complete left hemiplegia which a neurological consultant thought was caused by embolism of the lenticulo-striate artery due to rheumatic heart disease with auricular fibrillation. She became incontinent and emotionally unstable. Eight days later she suddenly developed signs of pulmonary infarction in the left upper lobe which subsided in two days. Three days later she suddenly developed marked blueness and paralysis of both legs, and pulsations in the dorsalis pedis and other leg arteries were not palpable. She died six hours later. Treatment consisted of digitalization and supportive management.

Comment. This case was undoubtedly one of embolism. The age, rheumatic history, auricular fibrillation with cerebral and pulmonary embolism are definite evidences of further embolism to the bifurcation of the aorta.

Case 7. G. S. (case of Dr. J. Hamilton Crawford), a white unemployed male, aged 65, was admitted in shock with a history of sudden collapse and vomiting with severe pains and paralysis of both legs. The pains began in the inguinal regions, shot down into the legs and were also present in the lower back. Three months before he collapsed with sudden pain in the left leg while walking. He had been getting intravenous injections for leg pains twice weekly at a hospital clinic.

Examination revealed a state of severe shock. There was exquisite tenderness over both lower quadrants and the hypogastrium. The extremities were blue, cold, and mottled and the femoral, popliteal and dorsalis pedis artery pulsations were not present. The reflexes were absent and there was a flaccid paralysis of the legs. Pain sensation was absent from the first to the fifth lumbar segments. Vibration sensation

was lost below the fourth lumbar segment and iliac crests. A diagnosis of saddle thrombus was made. Because of profound shock operation was deemed inadvisable. Despite papaverine and nitroglycerine intravenously every three hours, glucose by hypodermoclysis and other supportive measures, the patient died 18 hours after the onset. The admission temperature of 98° F. mounted to 104° terminally.

Autopsy revealed a heart that weighed 300 grams. The valves and heart cavities were negative. The aorta showed evidence of ulcerating atheromatous lesions in the thoracic portion. The lower portion of the abdominal aorta was completely occluded by a mass of light red soft thrombus markedly adherent to the wall, 7.5 cm. proximal to the bifurcation. The immediate wall was dark blue and calcified. Proximally, there was a characteristic long "currant jelly" clot. Both common iliac, hypogastric and external iliac arteries were markedly sclerotic and filled with the same material. On microscopy, there were atheromatous plaques with ulceration and adherent thrombi. Sections of the large arteries showed marked atherosclerosis with medial necrosis and occasional areas of slight round cell and histiocytic infiltration with endarteritis of several of the vasa vasorum. Final diagnosis was advanced atherosclerotic calcification with ulceration and complete thrombotic occlusion of the lower abdominal aorta, common iliac, external iliac and hypogastric arteries.

Comment. This case is obviously one of thrombo-arteriosclerosis of the aorta and large vessels with typical symptoms and findings. The process started three months previously with thrombosis of the left femoral artery with subsequent proximal occlusion to the bifurcation and then down the opposite common iliac and major branches. Operation was impossible because of profound shock.

Case 8. A. W., white female, aged 84, was admitted with spells of vomiting of six hours' duration. She was found on the floor screaming and vomiting foul brown material. Previous history was negative except for slight, old right facial paralysis.

Examination revealed negative cardiac findings. Blood pressure was 214 mm. Hg systolic and 138 mm. diastolic. There was abdominal tenderness with a suggestive mass in the left lower quadrant. Pelvic and rectal examinations were negative. The bladder was distended requiring catheterization. Diagnoses of carcinoma of the bladder or of mesenteric thrombosis were considered. She improved gradually and was to be discharged 25 days later when she developed a bilateral parotitis. Two days later the temperature suddenly rose to 104° F. and the patient went into coma and died. Terminally, she presented signs of a bilateral diffuse bronchopneumonia. Treatment was symptomatic.

Laboratory examinations included an electrocardiogram which showed left axis deviation and coronary sclerosis with marked myocardial degeneration. The Wassermann reaction was negative. The blood urea, creatinine and sugar were 98, 1.8 and 114 mg. per 100 c.c., respectively. The leukocytes were 13,250 per cu. mm. with 78 per cent polynuclears. The urine contained albumin (three plus) with occasional red and white cells and hyaline and granular casts.

Autopsy. The heart weighed 375 grams, the left ventricle was 2.5 cm. thick, but the valves and endocardium were negative. Just above the aortic valve there was a denuded area 2 cm. in diameter which contained soft debris and calcific flakes. Just above its bifurcation the aorta was distended by a fusiform swelling which on section was found to contain a thrombus of recent origin. Its posterior surface presented atheromatous plaques and ulcerations. The clot completely occluded the aortic lumen. Microscopy revealed typical atheromatous degeneration with recently superimposed thrombus formation. In addition, there were nephrosclerosis, generalized arteriosclerosis and bronchopneumonia. The extremities appeared normal in every respect.

Comment. This occlusion was caused by thrombosis superimposed on an arteriosclerotic aneurysm of the abdominal aorta. Although the patient presented no subjective or objective findings other than a suggestive mass in the left lower quadrant, there was a gradual thrombotic process which became rapidly occlusive just prior to death.

Case 9. H. T. (case of Dr. C. H. Greene), white female houseworker, aged 39, was admitted with a history of pains about the girdle and both lower extremities and weakness of the legs. She was irrational and confused.

Examination revealed flaccid paralysis of both lower extremities and bilateral foot drop. All reflexes and sensations were absent in the legs. There was muscle tenderness and pain on passive motion of the legs. The right leg was very cold below the knee, and the left leg was cold below the midleg. Later this extended irregularly to about the mid-thigh. The dorsalis pedis artery pulsations were not palpated. Following a neurosurgical consultation by Dr. J. Browder, three days later, it was thought that an occlusion of the abdominal aorta existed at the iliac bifurcation. The patient died without operation six days later because of the bilateral extent of the gangrene.

Laboratory studies revealed normal spinal fluid, blood chemical tests and Wassermann reactions. The white cell count rose from 38,900 to 66,300 (with 81 per cent polynuclear neutrophiles) in three days. The temperature was normal throughout. Roentgenographic examination suggested the presence of a left iliopsoas mass.

Autopsy. The heart weighed 520 grams and contained no thrombi or vegetations. Situated at the bifurcation of the aorta was a "saddle-back" thrombus extending 1¼ inches upward into the aorta, 2 inches into the right common iliac artery and 1 inch into the left common iliac artery, both of which were completely occluded. The thrombus was well organized, gray-white and very adherent to the intima. There was a bilateral abscess involving the lower fourth of the psoas muscles. A small tumor overlying the fifth lumbar vertebra proved to be a reticulum cell sarcoma which invaded this vertebra with secondary psoas abscesses. Other sections of the aorta presented myxomatous degeneration of the intima and media with organizing adherent thrombus. Significantly, the periaortic tissues exhibited septic thromboses of the capillaries.

Comment. The sequence of events in this case began with a small reticulum cell sarcoma which invaded the fifth lumbar vertebra. Microscopic sections proved that the aorta itself had not been invaded by the neoplasm. However, secondary infection with the formation of bilateral psoas abscesses produced both infection and pressure upon the aorta with resultant aortic thrombosis. The septic thromboses of capillaries in the periaortic tissues tend to bear out this observation. The age, normal valves, heart cavities and aorta, and negative history rule out an embolic or thrombo-arteriosclerotic origin.

Case 10. H. M., white female, aged 49, was admitted with a complaint of pains in both legs of five hours' duration. She was awakened by sudden stabbing, burning pains from the hips to the toes of both legs. They became blue, cold, then gray-white, with loss of all sensation except the excruciating pains. She had had auricular fibrillation five years previously and had been taking digitalis irregularly because of nausea. She had had scarlet fever at the age of eight but gave no other history of cardiorenal disease.

Examination revealed cardiac enlargement to the left with an irregular rate of 110 per minute. There were apical systolic and aortic diastolic murmurs and the sounds were of fair quality. The blood pressure was 168 mm. systolic and 108 mm. diastolic. Both legs were cold and mottled. The right leg was slightly less involved. All sensations were absent. No popliteal or dorsalis pedis artery pulsations were present in either extremity. A diagnosis was made of rider's embolus to the aortic bifurcation due to rheumatic heart disease with mitral insufficiency and stenosis, auricular fibrillation, class IV D. The patient was given large doses of papaverine, whiskey, aminophyllin and digitalis. She was also placed in a Sander's oscillation bed for six weeks constantly and was then able to get up and walk about, gradually and with assistance. This treatment was supplemented by a continuous temperature of 90° F. maintained by thermostatic-controlled light. Later she was given daily treatments with indirect ultra-short wave therapy to the lower back.

She began to show considerable improvement on the second day, with decreased intensity of pain and increased warmth. The legs became blue-red and sensation returned. There were no trophic changes. No pulsations were yet palpated in either popliteal or dorsalis pedis artery and in the left femoral artery. Four days after the onset, oscillometric readings showed none to be present in the left foot, leg and popliteal arteries. There was no dorsalis pedis pulsation on the right with a fibrillating swing of 4 to 8 in the tibial and popliteal arteries. The skin temperature showed a marked drop in the left limb. One month later there was noted marked blanching of the left foot with continued rubor of the right foot. On dependency, there was a lag with continued pallor for over 45 seconds, followed by no increase in pink color. The oscillometer showed no pulsations three days later. Skin temperature readings before and after the Landis-Gibbon test (temperature water 120° F. for 20 minutes) showed organic changes by the drop in skin temperature readings. Three weeks later these skin temperature readings presented a marked drop ranging from one to two degrees fall indicating a marked vasospasm. The oscillometric readings after the Landis-Gibbon test showed the same low or absent pulsations in the feet and left leg with some rise in the right thigh. One month later, examination revealed marked scaling of the right foot and toes. On elevation there was mild plantar ischemia on the left and pinkness on the right. On dependency, there was dusky cyanosis on the left and pallor on the right. The dorsalis pedis and posterior tibial pulsations on the right were present. The left dorsalis pedis was very faint and the left posterior tibial and femoral arteries were faint. She was able to walk alone without discomfort. Oscillometric readings showed marked improvement in pulsations indicating a canalization of the occluded vessels. The histamine test showed a delay in wheal formation up to five minutes on the left, but a fair reduction after 10 minutes indicating good surface circulation. In spite of the apparent subjective improvement there was a consistent fall in skin temperature following the Landis-Gibbon test which brought up the possibility of a marked spastic element. She was discharged two months after admission, greatly improved, with a final diagnosis of rheumatic heart disease with mitral insufficiency and stenosis, auricular fibrillation and embolism to the bifurcation of the aorta.

Further laboratory studies revealed normal Wassermann reaction, urinalysis and blood counts. The temperature course was normal throughout.

Comment. This case is remarkable in that recovery and recanalization occurred from an embolic process to the aortic bifurcation with intensive medical treatment that did not include surgery or heparin therapy. Measures that were vigorously applied included immediate use of large doses of papaverine, whiskey and aminophyllin, as well as such physical measures as the oscillation bed, controlled dry heat and remote ultra-short wave therapy.

The diagnosis of embolism to the aortic bifurcation due to auricular fibrillation is unquestioned because of the cardiac history, sudden bilateral leg involvement with pains from the hips down and absent pulsations in both legs noted by oscillometer recordings and Landis-Gibbon test. The gradual improvement was carefully noted with oscillometer and skin temperature recordings. At the present time the circulation of the extremities remains adequate.

Case 11. L. B. (case of Dr. D. M. McCarthy), white Italian male, aged 52, handy man, was admitted in an unconscious state with a history of a left sided "stroke" one year previously and again five months previously, causing him to be bedridden. There were no headaches or sphincter disturbances.

Examination revealed a left hemiplegia due to right middle cerebral artery thrombosis. Because of loss of vision in his right eye fundoscopy was done which revealed primary optic atrophy due to central retinal artery thrombosis. Blood pressure was 145 mm. systolic and 90 mm. diastolic. Two weeks later bronchopneumonia developed at both bases which cleared up with sulfapyridine therapy in four days. One week after this, it was noted that the patient suddenly seemed restless and complained of abdominal pains. Both legs developed coldness and a blotchy appearance and all arterial pulsations were lost in the legs. A diagnosis of possible saddle thrombosis was made. The following day both extremities continued to remain cold, cyanotic and pulseless. Before a surgical consultation could be undertaken the patient died suddenly on the third day. There was a temperature rise of two degrees terminally.

Laboratory Findings. Blood and spinal Wassermann reactions, colloidal gold test, blood and spinal fluid chemical findings and urinalysis were entirely normal.

Autopsy. The left leg was somewhat more swollen than the right. The heart weighed 350 grams. The valves were all competent. There were multiple infarctions of the kidneys. An old cerebral thrombosis was found. At the arch of the aorta about 4 cm. above the aortic cusps was a firm, raised, yellowish-pink vegetation firmly attached to an atheromatous plaque of the aorta and measuring 5 cm. in diameter. Elsewhere, the aorta was smooth and glistening except at the bifurcation, where there was a firm antemortem thrombus, 6 cm. long, closely adherent and extending about 4 cm. into both common iliac arteries. Microscopy revealed marked atherosclerotic degeneration. The intima was covered by a thin layer of fibrin and a recent antemortem thrombus which showed early basal organization. The media presented marked vascularization of the outer and middle thirds, and the adventitia showed marked fibrosis, vascularization and round cell infiltration.

Comment. This is a case of thrombo-arteriosclerosis of the aorta. Two areas of arteriosclerosis with superimposed vegetations were found in the ascending aorta and at the bifurcation. The cerebral, retinal and renal lesions were probably due to embolization from the former area of thrombo-arteriosclerosis. The saddle thrombus and the marked underlying atherosclerosis and similarity to the upper aortic process would rather speak for an arteriosclerosis with rapid thrombotic occlusion at this site.

Case 12. C. M., white female, aged 41, was admitted with complaints of sudden onset of cold, paleness and pain in both legs of 36 hours' duration. She also had abdominal and back pains and bloody urine. She gave a history of rheumatic heart disease for six years. She had edema and dyspnea for the past few years but she was not taking digitalis.

TABLE I

Case	Patient	Age	Sex	Past History	Location of Pain in Extremities	Other Symptoms	Findings Extremities	Other Findings	Positive Laboratory Findings	Wass.
				Symptoms			**Findings**		**Laboratory**	
1	F.O.	32	F	1) Mitral stenosis—at 21 yrs. 2) Rt. hemiplegia—6 mos. ago 3) Pulmonary infarction—2 wks. ago 4) Pulmonary edema—2 yrs. ago 5) Pain in L.U.Q. (splenic infarct)—2 yrs. ago 6) Embolus left leg—2 yrs. ago	None	R.U.Q. pain, vomiting	None	R.U.Q. tenderness B.P. 170/95	X-ray: prominent pulmonic conus EKG: Neg.	—
2	E.M.	34	F	Rheumatic joints—10 yrs.	Sudden onset excruciating pains both legs, paraplegia		Both legs cold, clammy, blue, absent pulsations of aorta below umbilicus, touch absent, pain and pressure increased	B.P. 150/70	EKG: right axis deviation X-ray: left side enlargement	—
3	J.H.	50	M	1) Arteriosclerosis extremities 2) Nephroptosis with nephrolithiasis	Pain both legs		Cold, reflexes and all pulsations absent	B.P. 130/90	X-ray: calcification iliac vessels	—
4	R.J.	62	F	1) Heart attack—6 mos. ago 2) Stroke—6 hrs. also 11 mos. ago	None		None	Sudden coma B.P. 160/110	EKG: Severe myocardial damage	—
5	E.B.	80	M	Bronchiectasis	None	Weakness cough	None	B.P. 140/70	EKG: myocardial damage	—
6	A.D.	38	F	Rheumatic history since childhood	Blueness and paralysis of both extremities		Absent pulsations both legs with marked blueness and absent reflexes	B.P. 120/80		—
7	G.S.	65	M	Treatment for arteriosclerosis of leg vessels—3 mos.	Severe pains in inguinal regions radiating down legs and lower back		Blue, cold, mottled, paralysis with absent reflexes and sensations. Tenderness over hypogastrium and both lower quadrants	Shock		
8	A.W.	84	F	Old right facial paralysis	None	Fecal vomiting	None	Suggestive mass in L.L.Q. B.P. 214/138	EKG: marked myocardial degeneration, left axis deviation. Blood urea 98 mg., leukocytes 13,200	—
9	H.T.	39	F	None	Pains about girdle and lower extremities with weakness legs		Flaccid paralysis both legs with absent sensation and reflexes. Gangrene both legs		Leukocytes 66,300	—
10	H.M.	49	F	1) Scarlet fever at 8 yrs. 2) Auricular fibrillation 5 yrs. ago	Sudden burning and stabbing pains from both hips to toes		Cold, mottled blue legs with no sensation or pulsations	B.P. 168/108	Oscillometer: no pulsations. Landis-Gibbon test: organic arterial occlusion	—
11	L.B.	52	M	Left hemiplegia—5 mos. and 1 yr. ago	None	Abdominal pain	Cold, cyanotic extremities without pulsations	Blindness right eye B.P. 145/90		—
12	C.M.	41	F	Rheumatic heart disease—6 yrs.	Cold, paleness and pain both legs	Bloody urine, abdominal and back pains	Absent pulsations, superficial gangrene, cold and mottling	Renal tenderness B.P. 110/60	Oscillometer: no pulsations. Urine: albumin, casts, red and white cells	—
13	L.F.	61	F	1) Rheumatic fever at 15 and 25 yrs. 2) Left hemiplegia—2 yrs. ago 3) Diabetes—4 yrs.	Sudden sharp pain in right thigh	Severe pain rt. lumbar, dizziness, profuse perspiration	Coldness up to umbilicus. Pulsations and sensation. Paraplegia absent	Rt. lumbar tenderness. Shock B.P. 176/70	Urine: albumin, sugar, red and white cells. X-ray: enlarged left ventricle and aortic arch with sclerosis EKG: auricular fibrillation after heart block	—
14	R.V.	47	F	1) Decompensation and rheumatic heart disease—for many years 2) Pulmonary infarction—1 month ago	Sudden onset sharp excruciating pain. Paralysis right leg		Complete absence pulsations both legs, marked cyanosis from hip to knee right leg with beginning gangrene below. Absent sensation rt. leg	B.P. 150/80	Urine: albumin, pus clumps Leukocytes: 14,000, 92% polynuclears	

TABLE I—*Continued*

Clinical Diagnosis	Other Diagnosis Considered	Heart Weight	Aortic Bifurc.	Common Iliac R	Common Iliac L	Ext. Iliac R	Ext. Iliac L	Int. Iliac R	Int. Iliac L	Etiology	Occlusion of Other Vessels	Clinical Diag. Corroborated	Duration of Acute Condition	Treatment
Rheumatic heart disease, auricular fibrillation, multiple emboli	Mesenteric thrombosis, peptic ulcer, acute cholecystitis, acute appendicitis	210	+	+	+					Embolus	1) Renal 2) Splenic 3) Sup. and inf. mesenteric 4) Left middle cerebral	No	11 days	Symptomatic digitalis
Rheumatic heart disease with embolization	None	360	+ Up to renal arteries	+	+	+	+	+	+	Embolus	Pulmonary artery	Yes	17 days	Oscillation bed, papaverine, dry heat
Post-operative saddle thrombus	None	360	+ Up to renal arteries	+	+	+	+	+	+	Thrombo-arteriosclerosis + post-operative thrombo-cythemia		Yes	1 day	Papaverine
Arteriosclerotic heart disease, left hemiplegia	None	425	+	+	+.				+	Thrombo-arteriosclerosis	Both middle cerebral arteries	No	2 days	Symptomatic digitalis
Bronchiectasis	None	280	+	+						Thrombo-arteriosclerosis		No	?	Symptomatic
Rheumatic heart disease with embolization, auricular fibrillation	None	—	No autopsy							Embolus	1) Lenticulo-striate artery 2) Pulmonary artery	No autopsy	6 hours	Papaverine, nitroglycerine, glucose clyses
Saddle thrombus	None	300	+	+	+	+	+	+	+	Thrombo-arteriosclerosis		Yes	18 hours	Symptomatic
Mesenteric thrombosis or carcinoma of bladder	Same	375	+							Mural thrombus + abdominal aneurysm		No	4 weeks	Supportive
Saddle thrombus	Tabes, cord tumor	520	+	+	+					Infection		Yes	6 days	Supportive
Rheumatic heart disease with auricular fibrillation and rider's embolus	None	—	Recovery by recanalization							Embolus		Recovered	2 mos.	Oscillation bed constantly continuous dry heat at 90°, papaverine, aminophyllin, whiskey, digitalis. Indirect ultra-short wave therapy
Saddle thrombus	Pelvic thrombo-phlebitis	350	+	+	+					Thrombo-arteriosclerosis	1) Central retinal artery—right 2) Middle cerebral artery 3) Renal arteries	Yes	2 days	Symptomatic
Rheumatic heart disease with auricular fibrillation and embolization	None	—	No autopsy							Embolus	Renal artery	No autopsy	5 days	Digitalis, dry heat, morphine
Rheumatic heart disease with auricular fibrillation and multiple emboli. Diabetes mellitus	Renal infection, later, rider's embolus	490	+	+	+	+	+	+	+	Embolus	Renal artery	Yes	16 days	Theophyllin, morphine
Rheumatic heart disease with auricular fibrillation and saddle embolus	None	—	No autopsy							Embolus	Pulmonary artery	No autopsy	4 weeks	Papaverine, cold packs

Examination revealed a heart slightly enlarged to the left. At the apex there was a presystolic thrill and rumble followed by a diastolic murmur and there was auricular fibrillation. Blood pressure was 110 mm. Hg systolic and 60 mm. diastolic. The liver was two fingers' breadth below the costal margin and the spleen was just palpable. There was marked renal tenderness. The left leg from the knee down was warm and swollen, with superficial gangrene of the medial and lateral aspects. The femoral, popliteal and dorsalis pedis arterial pulsations bilaterally were not palpated or heard. There was some precordial pain and dyspnea. Diagnosis made by the medical staff and surgical consultants was mitral insufficiency and stenosis due to rheumatic heart disease with auricular fibrillation. Embolization to the kidneys and aortic bifurcation with early gangrene of both legs were secondary, but embolectomy was deemed impossible because of the age of the condition. She was given morphine, dry heat and digitalis and died four days after admission.

Laboratory examinations included oscillometer recordings on admission, which revealed no thigh pulsations as compared with normal responses in the arm. Two blood cultures were negative. The blood urea and creatinine were 80 and 2.1 mg. per 100 c.c., respectively. Urinalysis repeatedly showed the presence of marked albuminuria, granular casts and many red and white blood cells. The temperature ranged between 100 and 104° F. Autopsy was refused.

Comment. The age, history of rheumatic heart disease, cardiac findings, congestion with auricular fibrillation, renal embolism, negative oscillometer readings and bilateral involvement of the extremities are indicative of further embolization at the bifurcation of the aorta.

Case 13. L. F., white female houseworker, aged 61, was admitted with severe pain in right lumbar region, dizziness and profuse perspiration for 24 hours. She had had diabetes for four years which was controlled by a 1500 calorie diet. She had had attacks of rheumatic fever at 15 and 25 years of age and was thereafter short of breath on exertion or lying down. She suffered a left "stroke" two years before and 10 days before developed a slight paralysis again.

Examination revealed the heart to be enlarged to the left with a loud blowing systolic apical murmur. The heart rate was 48 per minute and the blood pressure was 176 mm. Hg systolic and 70 mm. diastolic. There was pain and tenderness over the right iliac crest. In view of the finding of marked albuminuria and white and red cell clumps in the urine, a diagnosis of renal infection was considered. Two weeks after admission, the patient was seized with a sudden agonizing pain in the back of the right thigh, followed by coldness, blueness, paralysis and loss of sensation of both lower extremities. Auricular fibrillation and pulmonary edema occurred. No arterial pulsations were palpable. Dr. J. H. Crawford made a diagnosis of rider's thrombus preceded by renal infarction. The coldness extended to an area below the umbilicus corresponding to the tenth dorsal nerve root. In view of the profound shock and fibrillation, embolectomy was deemed impossible. Despite supportive therapy, aminophyllin and morphine the patient died the following day.

Laboratory findings revealed a negative Wassermann reaction and blood sugars ranging from 444 down to 286 mg. per 100 c.c. Urine sugars were two to three plus, after 30 units regular insulin daily. Blood urea and creatinine were normal. Roentgenographic examination revealed moderate enlargement of the left ventricle with sclerosis and enlargement of the aortic arch. Electrocardiographic tracing on admission exhibited auricular fibrillation, complete heart block with idioventricular rhythm and myocardial damage. This changed to slow auricular fibrillation ten days later.

Autopsy revealed marked obesity and generalized arteriosclerosis. The heart weighed 490 grams and contained no thrombi. The mitral leaflets were markedly thickened and retracted and the chordae tendineae were short and thickened. There were no vegetations or verrucae. The right kidney presented a large infarction. The aortic intima was smooth in the thorax, but below the diaphragm there were occasional yellow atheromatous areas with early calcification. Just above the bifurcation and extending bilaterally into the common iliac, external iliac and hypogastric arteries was a large completely occlusive antemortem thrombus which was firm, friable and clearly adherent to the wall. The other medium sized vessels were thin-walled and elastic. Microscopy revealed an antemortem thrombus in early stages of organization with slight calcification in the media. Final diagnosis was saddle thrombus, infarction of right kidney, chronic passive congestion of all organs and healed rheumatic mitral valvulitis with stenosis.

Comment. Despite the advanced age and early calcification of the aorta, this case is obviously of embolic origin. This is borne out by the rheumatic history, cerebral and renal emboli, cardiac findings with auricular fibrillation and bilateral involvement of the extremities. The additional influence of a markedly slowed blood stream as evidenced by the complete heart block and subsequent slow auricular fibrillation and terminal pulmonary edema allowed for a more rapid increase in thrombus formation. Embolectomy was impossible because of profound shock and pulmonary edema.

Case 14. R. V., white housewife, aged 47, was admitted with a history of sudden onset of excruciating pain in her right leg for two hours with absent sensation and inability to move the leg. Past history revealed that she had rheumatic heart disease with attacks of decompensation for many years. One month before she developed a pulmonary infarction.

Examination revealed moderate cardiac enlargement with a double murmur at the apex and auricular fibrillation. Blood pressure was 150 mm. systolic and 80 mm. diastolic. There were basal râles. There was complete absence of pulsations in both legs. Marked cyanosis of the right leg from the hip to the knee was present with complete blanching. Sensation was absent below the knee and the patient was unable to move her leg. A diagnosis of rheumatic heart disease with auricular fibrillation and embolization to the bifurcation of the aorta was made. The patient was given papaverine and cold packs to the extremity for the extreme pain as well as to decrease the local metabolism. A consultation by Dr. S. Silbert two days later corroborated the findings. The patient was then moved to another city where the condition became progressively worse with evidence of increasing intoxication. She died after one month. Autopsy was refused.

Laboratory examinations included a urinalysis which revealed an albuminuria with clumps of pus cells and a white cell count of 14,000 cells with 90 per cent polynuclear neutrophiles.

Comment. This case presents the typical picture of embolization due to rheumatic heart disease with auricular fibrillation. Pulmonary infarction occurred one month previously. The complete absence of all pulsations in both legs places the embolization at the bifurcation. But the symptoms and beginning gangrene of the right leg point to a complete occlusion of the right common iliac artery with partial obstruction of the left common iliac artery. Apparently there was a sufficient blood flow to prevent changes, despite absence of all pulsations.

ETIOLOGY

1. *Embolism* (50 per cent). The largest number of occlusions (seven cases) was due to embolism (table 2). All occurred in females ranging in age from 32 to 61 years of age (average age, 43 years) with the greatest number in the third decade of life. Without exception there were both a history and definite physical findings of rheumatic heart disease. In addition, all presented auricular fibrillation which caused emboli to be thrown from the left auricle to the aortic bifurcation. When the embolus itself was not large enough to occlude the aorta there undoubtedly occurred a more or less rapid antemortem thrombosis superimposed on the original nidus. Emboli were thrown off to other arteries in six of the seven cases. They were

TABLE II

	Male	Female	Total
1. Embolism (due to rheumatic heart disease with auricular fibrillation)		7	7
2. Thrombo-arteriosclerosis of aorta	4	1	5
3. Abdominal aneurysm with mural thrombosis		1	1
4. Infection		1	1
Total	4	10	14

the renal artery (three times), pulmonary artery (three times), cerebral arteries (two times) and the splenic, superior and inferior mesenteric arteries (once each). One unusually interesting case of embolization (H. M.) went on to recovery.

2. *Thrombo-Arteriosclerosis of the Aorta* (36 per cent). The term "thrombo-arteriosclerosis of the aorta" best indicates the underlying process of atheromatous degeneration and ulceration with superimposed thrombus formation. Five of our cases were in this category. The ages ranged from 50 to 80 years with an average of 62 years. The thrombo-arteriosclerotic group on the average were exactly 20 years older than the embolism group. However, the preponderance was among males in a five to one ratio. No more extensive occlusions throughout the aorta and its main branches occurred in this class than in the cases of embolism. However, occlusions of other arteries occurred more frequently in the embolic group than in the thrombo-arteriosclerotic group. In the former, other arteries were involved five out of six times. In the latter, only two out of five times. In one case (J. H.) a postoperative thrombocythemia was a secondary factor in the deposition of a thrombus since it began to form on an aorta that was markedly ulcerated by an atheromatous process immediately following operation.

3. *Abdominal Aneurysm with Mural Thrombosis* (7 per cent). It is a long accepted fact that in aneurysm of the abdominal aorta, death frequently results from a complete obliteration of the lumen by thrombi. An arteriosclerotic aneurysm just above the aortic bifurcation was found at autopsy in

a female of 84 years (A. W.). The Wassermann reaction was negative. There was hypertensive heart disease and a suggestive mass was palpated in the left lower quadrant. The gradually progressive thrombosis of the aneurysmal cavity became rapidly occlusive just prior to death.

4. *Infection* (7 per cent). In some infections, such as sepsis and typhoid, areas of degeneration may occur in the aorta. The intima or media is attacked and then acts as a focus for the formation of a thrombus. In one of our cases (H. T.) with a normal aorta and heart, bilateral iliopsoas abscesses secondary to a reticulum-cell sarcoma resulted in the formation of septic thromboses of capillaries in the periaortic tissues. This gave rise directly to an adherent thrombus. The aorta was not invaded by the malignancy. In addition, in inflammatory states there is a marked increase of the fibrinogen in the plasma and a decrease of the capacity of the blood to retain its corpuscles in suspension, thereby aiding coagulation. Essential thrombophilia as described by Nygaard and Brown[2] may conceivably, though extremely rarely, result in thrombosis of the aorta. It would be more likely to occur secondarily following splenectomy, or in polycythemia and myeloid or megakaryocytic leukemia.

AGE-SEX DISTRIBUTION

This condition occurred in all age groups past the third decade (table 3). In the younger age groups it has already been noted that the process was essentially embolic and occurred entirely among females. The thrombo-

TABLE III

Age-Sex Distribution

Age Group	Male	Female	Total
30–39		4	4
40–49		3	3
50–59	2		2
60–69	1	2	3
70–79			0
80–89	1	1	2
Total	4	10	14

arteriosclerotic group of aortic occlusions occurred in the older age groups and mostly among men (80 per cent). The case of abdominal aneurysm with mural thrombosis occurred in a female of 84 years, whereas the case due to infection occurred in a female of 39 years. The ratio of males to females in the entire series was 4 : 10.

SYMPTOMS AND FINDINGS

The 14 cases were divided into a group of 10 cases which were diagnosed and four which were not diagnosed. The former group is considered first.

The latter group can be considered more appropriately under causes for errors in diagnosis.

1. *Pain.* The typical symptoms of severe sudden pains in the extremities occurred in eight of the 10 cases (80 per cent). The pain at times radiated into the lower back, inguinal regions, or girdle area. When present it varied in intensity from slight to severe, and was described as excruciating, sharp, stabbing, dull or aching. Varying degrees of shock ensued four times.

2. *Temperature and color changes* were present 10 times (100 per cent). The color changes were variously described as black, cyanotic, mottled, blanched, blue, pale or white. Temperature changes were referred to as cold or clammy. Rarely was superficial gangrene or bleb formation noted.

3. *Pulsations* were noted as being absent eight times (80 per cent). In one case (E. M.) pulsations were correctly noted as being absent as far up as the umbilicus. At autopsy, the aorta was found occluded at the level of the fifth lumbar vertebra.

4. *Weakness of extremities* was present six times (60 per cent) and varied from slight weakness to more frequent complete loss of motion or paraplegia.

5. *Loss of sensation* was noted six times (60 per cent). Occasionally, the sensations were increased early but later were completely lost.

6. *Reflexes* of the lower extremities were noted as absent four times (40 per cent).

CAUSES FOR FAILURE IN DIAGNOSIS

A correct diagnosis was not entertained in four cases. The reason for such failures rested simply on the complete absence of any signs or symptoms pointing to occlusion of the aorta or blood supply of the extremities. This can be explained on the rapid formation of an occlusive process shortly before death when painful stimuli were not prominent while thrombus formation was more rapid because of slowed circulation and other factors previously described. There was insufficient time for visible changes to develop in the extremities or the patients went into sudden shock or coma and died very shortly thereafter. One case (F. O.) with vomiting and right upper quadrant pain and tenderness was variously considered as mesenteric thrombosis, peptic ulcer, acute cholecystitis or acute appendicitis. There proved to be an embolus at the aortic bifurcation extending into both common iliac arteries. Another case (R. J.) which proved to be a thrombo-arteriosclerotic occlusion, suddenly became comatose and died two days later. Despite a previous thrombosis of the left middle cerebral artery, no signs nor symptoms were present referable to the acute occlusion. A male of 80 years, with bronchiectasis, on the chronic service for one and a half years, revealed a similar process terminally. The last case (A. W.) also presented no symptoms or findings in the extremities but had fecal vomiting with a suggestive mass in the left lower quadrant which was interpreted as a carcinoma of the

bladder or mesenteric thrombosis. The occurrence of other embolic or thrombotic phenomena should arouse suspicion of the possibility of aortic occlusion. Oscillometer readings and Landis-Gibbon tests may be helpful. Platelet counts, plasma coagulation time and hyperglobulinemia may be of value in suspicious cases. Roentgenographic studies of abdominal aorta calcification or aneurysm with or without contrast media may also shed some light.

Duration of Life

Following the onset of the acute condition, the duration of life ranged from six hours to one month. The average period was 10 days. One case (H. M.) with recovery was discharged from the hospital two months later. There was no apparent difference in the duration of life of the embolic and thrombo-arteriosclerotic groups.

Treatment

None of our cases was subjected to embolectomy. Most frequently the patient applied for treatment too late or after gangrene became apparent. In other instances, shock, circulatory failure or failure of diagnosis precluded surgical intervention. Large doses of papaverine and other vasodilators, with digitalization when indicated was the treatment of choice. The oscillation bed was in continuous use in two cases, with favorable results in one. The latter (H. M.) was also given continuous dry heat at 90° F., large doses of vasodilators (papaverine, aminophyllin and whiskey) as well as digitalization. Indirect ultrashort wave therapy was added later. She recovered two months after such intensive treatment. The use of heparin to mitigate a progressive occlusion might be of great value. Its use in occlusions of arteries and veins has already been well established. When a person to be operated upon is known to have marked arteriosclerosis (as in case of J. H.) it may be advisable to increase the water content in the blood by abundant drinking, or by administration per rectum, since an excessive concentration of plasma protein favors the inception of thrombi. A diet low in protein reduces the fibrinogen content of the blood. These measures are of added importance when there are indications of cardiac decompensation, especially of auricular fibrillation and a history of previous attacks of thrombosis or embolism elsewhere.

Summary

1. Occlusions of the abdominal aorta are highly dramatic episodes that are usually due to embolism from auricular fibrillation or thrombo-arteriosclerosis. The former condition is prevalent among women and in an age group averaging 20 years younger and is associated usually with embolic phenomena elsewhere. It also may be caused by abdominal aneurysm with mural thrombosis or by massive infection. Secondary hemic factors such

as essential or post-operative thrombocythemia, dehydration, increased fibrinogen and globulin, or pressure and trauma may exert an additional influence.

2. Symptoms and findings in the order of frequency are varying degrees of temperature and color changes, pain, absence of pulsations, weakness or paralysis of extremities, loss of sensations and absent reflexes.

3. The reason for failure in diagnosis is the rapid antemortem formation of complete occlusion with no time for the development of the characteristic signs or symptoms, especially when painful stimuli are decreased ante mortem or following shock.

4. This condition is compatible with life up until one month, although the average period of life was ten days.

5. The possibility of embolization to the aortic bifurcation should be anticipated in every case of rheumatic heart disease with auricular fibrillation occurring among females, especially when emboli to other organs have already occurred.

6. It is well to remember that in some cases of thrombo-arteriosclerosis of the aorta, symptoms and findings referable to the lower extremities may not be due to the more common peripheral vascular diseases but rather to a slow thrombotic occlusion at the bifurcation of the aorta.

7. A case is presented of a patient who recovered, under conservative management, by recanalization of a rider's embolus occurring as a result of rheumatic heart disease with auricular fibrillation; complete observations were recorded.

CONCLUSION

Occlusion of the abdominal aorta should be strongly suspected when there is a sudden onset of pain of varying intensity in the lower extremities and pelvis with temperature and color changes, sensory disturbances, and weakness or paralysis. This possibility becomes greater when occurring in females with auricular fibrillation due to rheumatic heart disease, especially when signs of embolization have occurred in other organs. An early diagnosis may result in cure or arrest by surgical intervention (embolectomy), heparinization or other appropriate medical measures described herein.

ADDENDA

Two additional, interesting cases of saddle embolus diagnosed ante mortem occurred since this paper was submitted for publication. Two new factors are added: in the first case embolism from syphilitic aortitis, in the second case embolism from mural thrombus of myocardial infarction.

M. J., 46 year old white female, was admitted with progressive pain and occasional numbness in both legs for several weeks. In the preceding eight years she had had four epileptic convulsions. About the same time, she developed ptosis of the right eyelid and a two plus Wassermann reaction was discovered. About eight years

previously she had suffered an attack of paralysis, numbness and coldness of both legs, requiring seven weeks of bed rest. No cyanosis was noted and it cleared spontaneously. One week before admission, she noticed weakness in the right knee which soon spread to the ankle. The leg became numb and the next day it became cold. Since then both feet were cold most of the time.

Examination revealed negative findings except for the extremities. The skin over both legs and lower abdomen was cyanotic and cold. Pulses were unobtainable in the legs. Complete anesthesia was present up to both knees. Blood pressure was 160 mm. Hg systolic and 80 mm. diastolic. A diagnosis of thrombosis of the abdominal aorta and syphilis was made. The patient became rapidly worse, dying two days later, despite supportive therapy.

Autopsy revealed the heart to be entirely negative. It weighed 300 grams. There were no thrombi or ulcerations or other lesions. However, a syphilitic aortitis of the thoracic aorta was present. At the junction of the arch and descending portions, there were three firmly attached, small mural thrombi. One and a half inches above the bifurcation of the aorta was a large antemortem clot which completely occluded the lumen of the abdominal aorta. It extended into both common iliac arteries for two inches. Final diagnosis was mural thrombosis of the arch of the aorta with syphilitic aortitis; embolization to the bifurcation of the aorta with superimposed thrombosis.

Comment. In this unusual case, mural thrombi formed on the syphilitic involvement of the thoracic aorta. Since the heart, pulmonary veins and wall of the abdominal aorta were negative, it is fair to assume that there must have been embolization to the bifurcation with slow occlusion by superimposed thrombosis. This case, occurring in a female, is exceptional in that it is characterized by the absence of heart disease with fibrillation.

A. D., a white unemployed male, aged 44, complained of weakness, more marked on the right side, and pains in splenic, heptic and renal regions. The past history was entirely negative except for an accident 10 years previously when he was struck on the head, with resulting right-sided weakness.

Examination revealed a white, obese male in no acute distress, with weakness of the right side of the body. The mental processes were somewhat dull. The right half of the body and left side of the face were partially paralyzed. Heart sounds were of poor quality, regular, rate 120 beats per minute. Lungs were clear on percussion and auscultation.

Laboratory studies included an electrocardiogram which revealed a recent anterior coronary occlusion. The white cells numbered 23,400 per cu. mm. with 89 per cent polymorphonuclears and 10 per cent lymphocytes. Urinalysis disclosed a specific gravity of 1.016 with a trace of albumin and a few red cells per high power field. The temperature curve ranged between 99 and 102° F. with a terminal rise.

He complained of sudden severe pains in the thighs. Two days before death his extremities became slightly cyanotic, cold and numb up to the mid-thigh regions. The day of death his pulse became rapid and irregular and he entered a state of shock from which he failed to recover. Final clinical diagnosis was recent coronary occlusion and embolization to the bifurcation of the aorta and old cerebral accident.

Autopsy revealed no external evidence of disease or trauma except for slight atrophy of the left side of the body. Both legs were involved in a marked purplish discoloration completely encircling the mid-thigh region of both legs, slightly higher on the right. There was no edema or gangrene. Upon opening the aorta, only slight atheromatous degeneration was found in the thoracic portion but somewhat more marked toward the bifurcation. At the bifurcation of the aorta was found a saddle

embolus which was moderately adherent. It was partially organized and extended down the right common iliac as far as its bifurcation into its internal and external branches. The embolus with very slight difficulty exposed a lustreless, discolored endothelium. The embolus was especially adherent in the right common iliac artery. The surface beneath the embolus was not unduly thickened and there was no evidence of any atheromatous degeneration beneath (figure 1). Numerous embolic infarctions of the spleen and kidneys were evident. The heart weighed 470 grams. On

Fig. 1. Saddle embolus at bifurcation of aorta with extension into the right common, internal and external iliac branches. Although atheromatous plaques are noted, none was present beneath the embolus.

section the myocardium was soft, pale brown and on the left measured 2.5 cm., on the right 0.5 cm. At the apex of the heart was an adherent thrombus, the size of a walnut, which was gray and adherent to the anterior surface. The musculature beneath was thinned down sharply to 0.5 cm. in thickness and was discolored. The patch measured 6 cm. in diameter, involving the apex of the anterior surface and portions of the interventricular septum at the apex. The mouths were slightly contracted due to a fairly marked atheromatous degeneration about the sinuses of Valsalva. The coronary arteries were markedly thinned and sclerotic, being completely occluded approximately 2 cm. from the mouth of the left anterior artery. The pos-

terior coronary and branches were similarly sclerotic and narrowed but presented no evidence of thrombosis. The lungs weighed 1100 grams together. At the base of the right lower lobe, gray hepatization was present. In the ileum was a tremendous Meckel's diverticulum, measuring 12 cm. in length and 2.5 cm. in diameter. The brain was entirely negative.

Final diagnosis was recent myocardial infarction with superimposed mural thrombus of left ventricular apex, multiple infarctions of kidneys and spleen, saddle embolus of aorta and right common internal and external iliac arteries and early gangrene of both lower extremities.

Comment. This case is of special interest because the focus for embolization proved to be a recent myocardial infarction with embolization from the superimposed mural thrombus.

Following are two additional cases, both diagnosed ante mortem, with recovery in one on conservative management.

E. R., 84 year old white female, was admitted with complaint of sudden onset of blueness, coldness and pain in both lower extremities. She was semicomatose and further history was unobtainable.

Examination revealed absence of the right eye. The lungs presented moist râles, most marked in the left lower lobe. The heart was not enlarged but was fibrillating at the rate of 144 per minute. No murmurs were heard. The blood pressure was 160 mm. Hg systolic and 90 mm. diastolic. There was marked arteriosclerosis of all vessels. Both lower extremities were cold, mottled and cyanotic. Above the knees, however, the legs were warm and pink and the femoral arteries were definitely palpated. Diagnosis was thrombo-arteriosclerosis of the abdominal aorta and the popliteal arteries.

Laboratory studies included an electrocardiogram which revealed a 2:1 auricular flutter and left axis deviation. Chest roentgenogram presented marked calcification of the aortic arch and bronchopneumonia. Wassermann reaction was negative. Urea and creatinine were 81 and 3.1 mg. per 100 c.c. blood, respectively. Despite rapid digitalization and other supportive measures, the temperature rose and the gangrenous process progressed. Death occurred on the fifth day.

Autopsy revealed a markedly adherent, flattened, gray-red thrombus attached to a slight arteriosclerotic aneurysmal bulge, extending a distance of 6 cm. from below the opening of the superior mesenteric artery. The picture was typically that of thrombo-arteriosclerosis of the abdominal aorta. The abdominal aorta presented marked atheromatous degeneration with ulcerations. The mouths of the aortic branches were uninvolved. Both popliteal arteries contained two fairly recent emboli which had broken off from the aortic thrombus and completely occluded the lumina with resultant gangrene of the lower legs. In addition, there was arteriosclerotic heart disease and bilateral bronchopneumonia.

Comment. This case is of unusual interest because of the presence of both intravascular processes, thrombosis and embolization. The abdominal aorta was occluded by marked thrombo-arteriosclerosis which one finds in this age group. The lesion in the lower extremities was the result of emboli from this thrombotic area since they were not very adherent to the tibial arteries and were much redder than the abdominal thrombosis. Cardiac emboli due to fibrillation were ruled out at autopsy.

Despite cardiac arrhythmia, diagnosis was possible clinically because of the age, absence of murmurs, marked arteriosclerosis of all blood vessels

corroborated by roentgenogram, and bilateral gangrene. The most interesting feature, however, was the occlusive process in the abdominal aorta with embolization from this source. These skipped the bifurcation (absence of clot at this region and the presence of femoral pulsations clinically) and entered both popliteal arteries:

H. F., white unemployed male, aged 45 (case of Dr. Henry Wolfer) was admitted with excruciating pains in both legs of one day's duration. Paralysis, numbness and tingling of legs were also present. He had a history of rheumatic fever dating back 28 years. Nine years previously he developed infrequent attacks of epileptiform seizures. He had no edema, dyspnea or angina, but had exertional dyspnea for three years. An attack of right upper quadrant pain two weeks previously was diagnosed as ventral hernia, but operation was cancelled temporarily because of his cardiac condition.

Examination revealed a slightly obese male, somewhat apprehensive. The heart was slightly enlarged to the left with a presystolic murmur and thrill at the apex. There was no evidence of fibrillation and the rate was 80 per minute. Blood pressure was 150 mm. Hg systolic and 70 mm. diastolic. Lungs presented moist râles at both bases. There were no abdominal abnormalities noted other than a small ventral hernia above the umbilicus. Both lower extremities were cold from the midthigh to the toes. However, there was no gangrene and only slight cyanosis, indicating that the collateral circulation was still adequate. The right femoral artery was barely palpable and all other pulsations were absent. He was unable to move his legs. Diagnosis was rheumatic heart disease with mitral stenosis and saddle embolus to the aortic bifurcation.

Laboratory studies included oscillometry which revealed absent arterial pulsations below both knees and in the left thigh. The right thigh presented very weak waves. Electrocardiograms revealed sinus tachycardia with myocardial damage. Urea, creatinine and sugar were 32, 1.2 and 96 mg. per 100 c.c. blood, respectively. Urinalysis and blood studies were normal. Except for a rise to 103° F. on the third day, the temperature was always normal.

Therapy consisted of oscillating bed, an ampule of papaverine intravenously every four hours, 8 c.c. of heparin in a liter of 5 per cent glucose, intravenously. Heat was applied to the lumbar region. One week later the heparin was repeated and Buerger's exercises were added. General supportive measures, such as oxygen, hematinics and vitamin therapy, were added at intervals.

Course. One week later he was barely able to move his feet, but there was no cyanosis. One month later, he could move his right leg fairly well but his left leg moved only slightly with great difficulty. Six weeks later he was encouraged to try walking to aid further recanalization. Ten weeks later, his legs were warm and pink. No pulsations were palpable. This was expected since the collateral circulation, which develops after an occlusion of a major vessel, rarely, if ever, can be palpated or even measured oscillometrically. The oscillometer revealed only one-eighth in his left thigh. He entered the wheel chair stage after three months. Four months later, he developed an attack of pulmonary edema after straining at stool. This was relieved by phlebotomy. Five and one-half months after his attack he was able to walk about with great ease. Pulsations were still not palpable.

Comment. The presence of rheumatic heart disease with auricular fibrillation, the sudden onset of bilateral leg pains, numbness and paralysis, and the oscillometric findings all indicate the presence of saddle embolus. Collateral circulation and rapid recanalization produced adequate circulation.

It is difficult to evaluate the importance of heparin. In the other case, terminating in recovery, none was employed and recovery time was even shorter. However, when one views the tremendous mortality rate, every possible therapeutic agent should be employed. Perhaps further enlargement of the thrombus or embolism may be avoided. At any rate, its use should be encouraged in every case, since further thrombosis and embolism may thus be avoided.

BIBLIOGRAPHY

1. REICH, N. E.: Portal thrombosis occurring in portal hypertension, ANN. INT. MED., 1942, xvii, 270. Primary portal phlebosclerosis, Arch. Int. Med., 1942, lxix, 117.
2. NYGAARD, K. K., and BROWN, G. E.: Essential thrombophilia, Arch. Int. Med., 1937, lix, 82.

THE SIGNIFICANCE OF JOINT PAINS CAUSED BY STERILE STREPTOCOCCUS TOXIN *

By Paul S. Rhoads, M.D., F.A.C.P., and Melvin L. Afremow, M.D.,
Evanston, Illinois

In 1937 Healey [1] reported that about 3 per cent of young adults being immunized against scarlet fever developed multiple joint pains as a reaction to one or more injections of the sterile filtrate of broth cultures of scarlet fever streptococci. She noted that the majority of persons who had this reaction gave a history of previous joint pains associated with rheumatic fever, or of streptococcus infections of the nose and throat. We had made similar observations. Healey showed that 74.6 per cent of a group of 63 such persons which she studied did not have joint pains when injected with the same dose of streptococcus filtrate which had been heated, and that 17.4 per cent had some joint pains but milder ones when given the heated material. Her conclusion was that the majority of such reactions were caused by the toxin in the filtrate rather than the protein of the streptococci or the culture medium.

Coburn and Pauli [2] studied in various ways 40 strains of hemolytic streptococci cultured from 38 rheumatic subjects during pharyngeal infections. About half were effective in reactivating the rheumatic process. The only constant characteristics of the effective strains were that they were stronger in streptolysin than the non-effective strains and that practically all produced toxin in broth cultures giving good skin reactions in dilutions of 1:50 or 1:100 in Dick positive persons.

The above studies prompted us to investigate the health performance of a group of student nurses who had multiple joint pains as a reaction to one or more immunizing doses of scarlet fever toxin. They were considered particularly suitable subjects because they are frequently exposed to hemolytic streptococcus infections. During the years 1934 to 1940, a group numbering 181 was found to have reported this reaction. Their health records were carefully tabulated. An equal number of nurses who were similarly immunized but reported no joint pains as a reaction to the doses were chosen from the records of each year as a control group. The results are tabulated in tables 1 and 2. It will be seen that the average period over which the health observation was recorded was well over a year per nurse in both groups. The average duration of time on duty was 83 days less per nurse in the "joint pain" group than in the control group. Many factors may enter into this difference but doubtless the most important was that

TABLE I

Health Performance of Nurses Who Had Active Immunization Against Scarlet Fever

	Nurses Who Had *Joint Pain* as Reaction to Scarlet Fever Toxin (181 in group)	Nurses Who Had No *Joint Pain* as Reaction to Scarlet Fever Toxin. *Controls* (181 in group)
Total days of duty	86,597 (av. 478.4 per nurse)	101,546 (av. 561.0 per nurse)
Days off duty because of reactions to immunizing doses of scarlet fever toxin	451 (av. 2.5 per nurse)	107 (av. 0.6 per nurse)
Total days off duty due to illness	4,953 (5.7% of time on duty)	3,669 (3.6% of time on duty)
Days off duty due to respiratory infections including tonsillitis, pharyngitis, sinusitis, bronchitis, etc., but not including pneumonia	2,357 (47.6% of total illness). 166 nurses affected	1,825 (49.7% of total illness). 148 nurses affected
Days off duty due to "rheumatic fever," "rheumatic heart disease," "arthritis," "muscle pains," erythema nodosum	426 (8.6% of total illness). 28 nurses affected. Av. 15.2 days per nurse	145 (3.9% of total illness). 18 nurses affected. Av. 8.1 days per nurse
Number of nurses sent home because of illness	34 (18.8% of group)	19 (10.5% of group)
Number of nurses sent home because of rheumatic affections	17 (9.4% of group)	5 (2.8% of group)

TABLE II

Objective Evidence of Rheumatic Heart Disease in Groups Studied

	Nurses Who Had *Joint Pain* as Reaction to Scarlet Fever Toxin (181 in group)	Nurses Who Had No *Joint Pain* as Reaction to Scarlet Fever Toxin. *Controls* (181 in group)
Results of physical examination on entrance to training. Systolic or presystolic apical murmur, cardiac enlargement, ectopic beats	19	18
Number who presented evidence of progressive heart damage in association with attacks of rheumatic fever, arthritis or respiratory infection. (This evidence included in every case two or more of the following findings: premature contractions, auricular fibrillation, fresh cardiac murmurs, enlargement, prolonged tachycardia)	21	10

nearly twice as many nurses were sent home because of illness in the "joint pain" group as in the control group. It is interesting that 17 of the 34 nurses in the "joint pain" series who were returned to their homes because of illness were disabled by rheumatic affections, whereas only five of the 19 nurses in the control group who were sent home had rheumatic disease. Of course, the *total* time loss of these nurses is not recorded because they were not followed further.

It is seen that respiratory infections sufficiently severe to keep them off duty occurred in the majority of the nurses in both groups and accounted for nearly half the time loss from illness in both groups. However, the total time loss from them was greater in the "joint pain" group than in the control group. Rheumatic affections denoted by the diagnoses of "rheumatic fever," "rheumatic heart disease," "arthritis," "muscle pains," and "erythema nodosum" which in practically every instance were initiated by respiratory infections caused three times as much disability in the "joint pain" group as in the controls. As noted above, the *total* disability caused by these diseases is not indicated by the figures given because practically all of those diagnosed "rheumatic fever" or "rheumatic heart disease" were returned to their homes. The time loss due to other affections than those comprised in the respiratory and rheumatic groups was again in favor of the control group, but the difference was much less, the ratio being 2170 days in the "joint pain" group to 1699 days in the controls.

A history of "rheumatic fever," "rheumatic heart disease" or "arthritis" prior to coming to Cook County Hospital was four times as frequent in the "joint pain" group as in the controls. On the other hand, the history of previous attacks of tonsillitis was more frequent in the controls (64 times) than in the "joint pain" series (58 times). The experience with tonsillectomy had been practically the same, 107 (59.1 per cent) of the "joint pain" group having had their tonsils removed, and 110 (60.8 per cent) of the controls. In a large percentage of both groups tonsils had been incompletely removed.

That continuing infection was more common in the "joint pain" group than in the controls was evidenced by the fact that in routine cultures of the nose and throat to discover carriers in nurses on duty at Children's Hospital and on cultures in the nurses' infirmary, hemolytic streptococci were cultured 70 times in the "joint pain" group and 32 times in the control group.

The table on objective heart findings is self explanatory. The findings on physical examination are not considered by any means to be the only evidence of heart disease, but they are presented as recorded. Cardiograms were rarely made at that time. It is seen that the two groups were practically equal in the number who presented cardiac murmurs, irregularities of rhythm or enlargement, on entrance physical examination.

The figures on those having evidence of progressive heart damage in association with subsequent respiratory or rheumatic infections may be quite inaccurate. The discovery of a systolic murmur during the course of such infections in subjects in which a similar finding had not been recorded on the original physical examination was never taken as evidence of progressive heart damage unless it was found in association with one or more other significant findings such as pathologic arrhythmias, enlargement, persistent tachycardia, signs of decompensation, etc. It is seen that such evidence of progressive changes in the heart was twice as common in the "joint pain" group as in the controls.

CONCLUSION

Our observations support the view that a type of sensitiveness to hemolytic streptococcus toxin is present in a high proportion of persons who have had rheumatic infections or who harbor chronic streptococcus infections, which is not present in other persons.   It is manifested by the development of joint pains when streptococcus toxin is introduced into their tissues.   Such persons appear to develop rheumatic affections such as heart disease, polyarthritis and erythema nodosum more frequently than other persons not similarly sensitized.

BIBLIOGRAPHY

1. HEALEY, CLAIRE E.: The cause of joint pain occurring during immunization with scarlet fever streptococcus toxin, Jr. Am. Med. Assoc., 1937, cviii, 628.
2. COBURN, A. F., and PAULI, R. H.: Studies in the immune response of the rheumatic subject and its relationship to activity of the rheumatic process. IV. Characteristics of strains of hemolytic streptococci effective and non-effective in initiating rheumatic activity, Jr. Clin. Invest., 1935, xiv, 766.

DUPLICATE MEASUREMENTS OF CIRCULATION TIME MADE WITH THE SACCHARIN METHOD *

By Kurt H. Esser, M.D., and Kurt Berliner, M.D., *New York, N. Y.*

Measurements of the velocity of blood flow, repeated at intervals on the same patient, are sometimes used to evaluate the treatment of congestive heart failure. It is obvious that such serial tests can be of value only if their results chiefly reflect changes in the degree of heart failure and are not materially influenced by other factors. That such extracardiac factors are operative has recently been proved by Lilienfeld and Berliner [1] who used alpha lobeline hydrochloride as an agent and found wide "spontaneous" variations in the results of duplicate measurements. The present study was undertaken to determine whether duplicate measurements of circulation time made with a more commonly used agent, saccharin, show similar variations.

Material and Method. Sixty patients were used in this study, 56 males and four females, ranging in age from 14 to 66 years. Twenty-six were patients suffering from various forms of heart disease; 16 of these showed signs of congestive heart failure. The remaining 34 patients showed no evidence of heart disease, but were suffering from the various conditions commonly encountered in a medical ward.

The saccharin test was performed twice on each patient, with an interval of one hour, during which the patient was at complete rest. The technic of the test as described by Fishberg, Hitzig, and King [2] was closely followed. Thirty-one duplicate tests were made under ordinary ward conditions; 29 duplicate tests, on the other hand, were made with the patients under so-called "basal" conditions, the patients being prepared exactly as for a basal metabolism test. In each case the results of the first and second tests were compared, and the difference was expressed in per cent of the first test. An example: first test 14.2 sec., second test 22.0 sec., difference 7.8 sec., or 54.9 per cent.

Results. The results of the duplicate tests are shown in table 1. They were identical or differed by less than 1 per cent in only six cases; in the remaining 54 cases differences varying from 1 per cent to 143 per cent (2 to 39 sec.) were found. In the majority (35) of the duplicate tests, differences greater than 10 per cent were obtained (table 2). The differences were greatest in the group of patients suffering from congestive heart failure, whereas in patients with heart disease, but without congestive failure, and in patients free from heart disease, the differences were generally of a lesser degree.

Table 3 shows how the "basal" condition of the patient affected the differences between duplicate tests.   In all three groups, non-cardiacs, cardiacs with heart failure, and cardiacs without heart failure, the variations between tests were markedly smaller than in the corresponding groups who were in non-basal condition, in other words, the results were more accurate; yet even in the basal group variations up to 55 per cent occurred.

It should be mentioned that the differences between tests varied in both directions: the second test yielded higher results almost as frequently (23 cases) as it yielded lower ones (31 cases).

TABLE I

Case No.	Diagnosis	Result of first test (seconds)	Result of second test (seconds)	Difference (seconds)	Difference expressed in per cent of first test
	I. Patients not in "basal" condition.				
	A. *Patients without heart disease:*				
1	Pneumonia	19.5	19.0	0.5	−2.6%
2	Gonorrheal arthritis	21.6	21.0	0.6	−2.7%
3	Cirrhosis of liver	14.5	17.0	2.5	+17.2%
4	Pneumonia	12.5	12.5	0	0%
5	Pneumonia	15.4	24.0	8.6	+55.8%
6	Infectious arthritis	13.5	15.5	2.0	+14.7%
7	Lung abscess	27.0	14.2	12.8	−47.4%
8	Peptic ulcer	14.8	14.3	0.5	−3.4%
9	Rheumatic fever without carditis	16.5	12.5	4.0	−24.1%
10	Pneumonia	16.5	17.0	0.5	+3.0%
11	Pulmonary tuberculosis	32.0	26.2	5.8	−18.1%
12	Pneumonia	18.0	23.0	5.0	+27.8%
13	Gonorrhea	28.4	20.4	8.0	−28.2%
14	Dry pleurisy	13.5	12.5	1.0	−7.4%
15	Pleurisy with effusion	12.1	14.2	2.1	+17.3%
16	Pernicious anemia	17.5	24.5	7.0	+40.0%
17	Peptic ulcer	16.0	17.3	1.3	+8.1%
18	Pneumonia	22.4	39.0	16.6	+74.1%
19	Malaria	18.3	24.2	5.9	+30.6%
20	Bronchiectasis	17.0	14.0	3.0	−17.6%
21	Gonorrheal arthritis	23.8	19.6	4.2	−16.9%
	B. *Patients with heart disease without heart failure:*				
22	Rheumatic carditis-heart block	20.1	18.8	1.3	−6.4%
23	Hypertensive heart disease	13.1	14.8	1.7	+13.1%
24	Hypertensive heart disease	21.0	31.0	10.0	+47.5%
25	Hypertensive heart disease	17.0	16.5	0.5	−2.9%
26	Hypertensive heart disease	18.0	17.5	0.5	−2.8%
	C. *Patients with heart disease in congestive heart failure:*				
27	Luetic aortitis	46.2	43.0	3.2	−6.1%
28	Hypertensive heart disease	27.0	65.5	38.5	+142.5%
29	Coronary sclerosis	24.5	32.0	7.5	+30.6%
30	Hypertensive heart disease	31.5	31.2	0.3	−1.0%
31	Coronary sclerosis	28.6	21.5	7.1	−24.8%

TABLE I (*Continued*)

Case No.	Diagnosis	Result of first test (seconds)	Result of second test (seconds)	Difference (seconds)	Difference expressed in per cent of first test
	II. Patients in "basal" condition.				
	A. *Patients without heart disease:*				
32	Pneumonia	17.6	17.7	0.1	+0.6%
33	Pulmonary tuberculosis	29.5	27.5	2.0	−6.7%
34	Pneumonia	16.8	16.8	0	0%
35	Peptic ulcer	30.4	31.8	1.4	+4.6%
36	Ulcerative colitis	14.2	16.0	1.8	+12.7%
37	Pneumonia	15.0	14.1	0.9	−6.0%
38	Pertussis	11.8	14.1	2.3	+19.0%
39	Pneumonia	14.2	22.0	7.8	+54.9%
40	Peptic ulcer	15.0	14.9	0.1	−0.7%
41	Pneumonia	19.0	19.0	0	0%
42	Pneumonia	20.6	17.6	3.0	−14.6%
43	Pneumonia	18.2	14.0	4.2	−23.0%
44	Sickle cell anemia	28.2	22.4	5.8	−20.9%
	B. *Patients with heart disease without heart failure:*				
45	Hypertensive heart disease	18.5	18.0	0.5	−2.7%
46	Coronary sclerosis	26.6	25.1	1.5	−5.6%
47	Coronary sclerosis	44.0	39.0	5.0	−11.4%
48	Rheumatic pericarditis	13.6	15.1	1.5	+11.1%
49	Rheumatic carditis	17.0	17.0	0	0%
	C. *Patients with heart disease in congestive heart failure:*				
50	Coronary sclerosis	27.8	25.0	2.8	−10.2%
51	Coronary sclerosis	31.2	21.0	10.2	−32.1%
52	Purulent pericarditis	29.0	33.0	4.0	+13.7%
53	Coronary sclerosis	22.0	21.0	1.0	−4.5%
54	Coronary sclerosis	24.0	29.0	5.0	+20.8%
55	Hypertensive heart disease	27.0	25.0	2.0	−7.4%
56	Luetic aortitis	19.0	23.0	4.0	+21.0%
57	Hypertensive heart disease	21.0	19.0	2.0	−14.2%
58	Hypertensive heart disease	19.0	23.0	4.0	+21.0%
59	Coronary sclerosis	20.2	19.3	0.9	−4.4%
60	Coronary sclerosis	34.0	25.0	9.0	−26.0%

COMMENT

An analysis of tables 1 and 2 shows that considerable differences between results of duplicate tests were the rule, and that agreement was the exception. How can these differences be explained?

Variations in technic undoubtedly accounted for minor differences in results. Special care was taken to make the technical conditions (gauge of needle, size of syringe, position of patient's arm) identical in each pair of tests. The injections, on the other hand, could not always be given with exactly the same speed, and the same vein could not always be used for both injections.*

* In the saccharin test, in which the bulk of the injected material is fairly large (nearly 3.5 c.c.), these factors will play a greater part than in the lobeline test in which minute amounts are employed.

Slight differences in technic, however, cannot possibly account for the major variations in results which commonly occurred in this study. There are other and more important reasons why duplicate measurements of circulation time may yield varying results, no matter what method is used. It is well to remember that the results of circulation time measurements made

TABLE II

60 Duplicate Measurements—Differences in Results of First and Second Tests, Expressed in Per Cent of First Result

No difference in results (or less than 1%)	Difference less than 10%	Difference less than 20%	Difference less than 30%	Difference less than 50%	Difference less than 100%	Difference more than 100%
6 cases	19 cases	15 cases	10 cases	6 cases	3 cases	1 case

with saccharin represent velocity of blood-flow plus reaction time. Variations in reaction time may have occurred among our patients; but if they did occur, they were unpredictable. It might, for instance, have been expected that the experience with the first test would cause a prompter response to the second test in a substantial number of cases; such "conditioning," however, was not reflected in our results, as the second circulation time was longer almost as often as it was shorter.

As regards the actual velocity of blood-flow, this velocity is, first of all, affected by changes in cardiac function. In our series, however, a short time

TABLE III

60 Duplicate Measurements—Average Per Cent Difference Between First and Second Tests

	Patients not in "basal" condition	Patients in "basal" condition
Patients without heart disease	21.8% (4.3 sec.)	12.6% (2.3 sec.)
Patients with heart disease, but without heart failure	12.5% (2.8 sec.)	6.2% (1.7 sec.)
Patients with heart disease in congestive heart failure	41.0% (11.3 sec.)	15.9% (4.1 sec.)

interval between duplicate tests was deliberately chosen so that marked changes in cardiac function were not apt to occur. Velocity of blood-flow is, of course, known to be influenced by numerous other factors, e.g., exercise, excitement, digestion, fever, basal metabolic rate, hemoglobin content, volume of circulating blood, vitamin B_1 deficiency, and pathological states of the vascular system. Certain of these factors may have been operative in our series, and may have caused changes in the velocity of blood-flow even though the interval between tests was short. An observation which supports this view is that patients in "basal" condition showed smaller differences between tests than those not so prepared. This observation leads us to the con-

clusion that the saccharin test should always be performed with the patient in a "basal" condition.

The literature on duplicate measurements of circulation time was recently reviewed [1] and, therefore, need not be discussed here. One point, however, deserves reëmphasis, namely, that duplicate measurements of circulation time show the greatest variations in patients suffering from congestive heart failure. This was found by several investigators,[1, 3, 4] and has been clearly confirmed by our own studies, as here reported. Among non-cardiacs and cardiacs without congestive failure considerable differences occurred occasionally, but the average difference between tests was definitely greatest in the congestive heart failure group. These differences were greater not only in seconds—which was to be expected—but were greater when expressed in per cent. The observation is of practical significance because circulation time tests are most frequently performed on patients suffering from heart failure; in other words: they are least reliable in the very cases in which they are most needed. The conclusion is clear that serial tests made with the saccharin method should not be relied on to evaluate the progress of a patient in congestive heart failure, unless the changes shown by these tests are marked.

SUMMARY

1. Sixty duplicate measurements of circulation time were made with the saccharin method. The time interval between tests was always one hour.

2. Considerable differences between the results of the duplicate tests were frequently found. In only six cases were identical results obtained; in the remaining 54, differences varying from 1 per cent to 143 per cent (two to 39 seconds) were found. The result of the second test was higher almost as often as it was lower.

3. Thirty-one of the 60 duplicate measurements were made with the patients in "basal" condition. The differences between results of duplicate tests in this group were generally smaller than in the group of 29 patients who were not in "basal" condition.

4. The average difference in results of duplicate tests was greatest in patients suffering from congestive heart failure.

CONCLUSIONS

1. The saccharin test should be performed with the patient in a "basal" condition.

2. Serial circulation time tests with the saccharin method should not be relied upon to evaluate the progress of a patient in congestive heart failure unless the changes shown by these tests are marked.

BIBLIOGRAPHY

1. LILIENFELD, ALFRED, and BERLINER, KURT: Duplicate measurements of circulation time made with the alpha lobeline method, Arch. Int. Med., 1942, lxix, 739.
2. FISHBERG, ARTHUR M., HITZIG, WILLIAM H., and KING, FREDERICK H.: Measurement of circulation time with saccharin, Proc. Soc. Exper. Biol. and Med., 1933, xxx, 651.
3. TARR, LEONARD, OPPENHEIMER, BERNARD S., and SAGER, ROBERT V.: The circulation time in various clinical conditions determined by the use of sodium dehydrocholate, Am. Heart Jr., 1933, viii, 766.
4. WEISS, SOMA, ROBB, GEORGE P., and BLUMGART, HERRMANN L.: The velocity of blood flow in health and disease, Am. Heart Jr., 1929, iv, 670.

GOLD THERAPY IN RHEUMATOID ARTHRITIS *

By Alvin E. Price, M.D., F.A.C.P., and Bruno Leichtentritt, M.D.,
Detroit, Michigan

THE use of gold in the treatment of rheumatoid arthritis has become increasingly popular during the past 10 years. Since the original papers of Landé [1] and Pick,[2] and the subsequent, more extensive studies of Forestier,[3] numerous series of cases attesting to its value have been reported in both the European and American literature. A collective review has been published recently by Cecil et al.[4] In 1936 the use of gold was instituted in the arthritic service of the Wm. J. Seymour Hospital, Eloise, Michigan, and three years later it was introduced at Harper Hospital, Detroit, Michigan. During the early part of our experience with this form of therapy, favorable symptomatic results were obtained in many instances. After continued observation of these patients, however, relapses were frequently observed so that a different interpretation of our results became necessary. It seemed desirable, therefore, to continue our observations for a longer period of time before publishing our results.

The report which follows is concerned with an analysis of the results of gold therapy on 101 roentgenologically studied cases observed during 1936–1942. For an evaluation of the late results, a follow-up study on 81 available subjects of this series is included.

DESCRIPTION OF CASES

Of the 101 patients of this series, 95 were white and only six were negroes. Sex distribution was about equal between males (52) and females (49). These patients ranged in age from 20 to 81 years, with 55 per cent over 50 years at the time therapy was instituted. Not included in the final analysis of therapeutic results are 35 additional patients who, for various reasons, did not complete a full course of treatments. Seventeen of these discontinued treatment voluntarily; in 18, therapy was interrupted because of toxic reactions which will be discussed below.

All cases included in this clinical analysis have been classified into three groups according to the severity of the arthritic process. (a) In the *mild group* are included 14 patients (13.8 per cent) in whom the disease was confined to the periarticular soft tissue structures, with very little or no bony change demonstrable by roentgenogram. With only one exception, this entire group of patients was ambulatory. (b) In the *moderately advanced* group (30 cases—29.7 per cent) the joint disease was more extensive; some destruction of cartilage and limited ankylosis were present in several instances. Eight of this group of patients were bedfast. (c) Among the

severe cases are included 57 patients with multiple joint involvement and extensive ankylosis and deformity; roentgenographic evidence of marked decalcification of the bony structures of one or more joints and loss of the intra-articular space was present. In this group are included three cases of ankylosing spondylitis with associated involvement of the peripheral joints. Two patients with "mixed arthritis" are also included. Ninety per cent of the patients of this group were bedfast, many for years in the same institution.

GOLD TREATMENT

Gold sodium thiomalate (myochrysine) was used in 91 patients and gold thio-glucose (solganol-B oleosum) in 10 patients; gold sodium thiosulphate was used in two cases to complete courses started with myochrysine.* The sodium thiomalate and thio-glucose preparations were given intramuscularly; gold sodium thiosulphate intravenously.

The *dosage* of myochrysine varied throughout the six year period covered by this report. During the earlier part of the study 100 mg. were given weekly for a total of 18 to 20 weeks; subsequently, this dosage was given twice a week in a limited number of patients. In 1940 this was reduced to 50 mg. per week and more recently the dosage was further diminished to 25 mg. In most instances the latter dose was given twice weekly. The total amount of gold sodium thiomalate administered in one course has, therefore, varied from 0.5 gm. to 4 gm. Gold thio-glucose was given in ascending amounts starting with 10 mg. twice weekly and increasing successively to 25, 50, and 100 mg. until 1.2 grams were administered in a total of 21 injections. After an interval of two to six months a second course was given in about two-thirds of the cases; 40 patients received only one course, all others receiving from two to six courses. The total dose of drug administered varied from 0.5 gm. to 9.0 gm.

OTHER TREATMENT

More than one half of the patients in the series were confined to bed in the hospital at the time therapy was started. Most of these remained in bed throughout the first course. Physiotherapy consisting of baking and massage was given to most patients at some time during the course of gold therapy. It should be emphasized that these treatments were given so infrequently as to preclude any significant effect on the course of the disease. Focal infection, whenever present, was eradicated routinely before aurotherapy was instituted. Such therapeutic measures as vaccines, sulphur, vitamin D, and bee venom were given to a few patients before gold therapy was started. In each case, sufficient time had elapsed to nullify any effect which might have resulted from these measures. Artificial fever therapy

* Myochrysine was withdrawn from the market for a short period of time by the manufacturers.

was given to three patients between courses of gold. Analgesics, consisting principally of salicylates with occasional small doses of codeine, were used when necessary. Orthopedic measures such as traction, supporting splints, wedging casts and molds were used in a limited number of cases requiring such corrective procedures. More radical surgical interference, such as manipulation and various joint operations, were also used in several cases.

Precautions Observed during the Administration of Gold

Because of previously emphasized dangers of chrysotherapy, frequent observations were made for the appearance of untoward effects. The following routine was established: (1) frequent inspection of skin and mucous membranes; (2) urinalyses at weekly intervals; (3) hemoglobin determination, erythrocyte, leukocyte and platelet counts at weekly intervals in most cases; (4) icteric index determinations. Gold therapy was discontinued whenever toxic effects were indicated by these reactions, although in several instances it was resumed after apparent recovery.

Toxic Reactions to Gold

Some form of toxic reaction occurred in 38 per cent of all patients who were started on gold therapy. Except in one instance in which the patient received 25 mg. of gold sodium thiomalate, all toxic reactions observed followed the administration of large doses.

Dermatitis. A skin reaction of some degree was observed in 30 cases (25 per cent). This varied from simple erythema to extensive papulo-squamous eruptions involving the entire body. Severe exfoliative dermatitis was not observed. In two instances the skin lesion consisted solely of a fine desquamation of the eyelids. Pruritus was frequently present without an associated rash, though in the absence of the latter, therapy was not discontinued. All eruptions seen, with one exception, occurred in patients receiving gold sodium thiomalate. The rash appeared not later than after the fifth injection in over two-thirds of the cases; in 10 of these it occurred before the fourth. It appeared during the first course in all but two instances and reappeared in a subsequent course only once. In most instances it lasted not longer than two weeks although in one patient it recurred intermittently during a period of four months. The minimum amount of drug administered before the development of the rash was 50 mg. In three-fourths of the cases this did not exceed 500 mg. In the past two years, during which very small doses of gold were given, dermatitis developed in only one case. Residual pigmentation of the skin after complete clearing of the rash has not been observed. Histological study of the erythematous skin showed dilatation of the capillaries in the papillary layer with associated edema and infiltration by lymphocytes, plasma cells, and histiocytes. Psoriasis, present in three patients, was not considered a contraindication to the administration of gold, although a definite exacerbation of this condition was observed

shortly after starting the drug. Alopecia occurred in one case after the patient had received approximately one gram.

Mucous membrane lesions, consisting principally of superficial ulceration of the buccal mucosa, occurred in four cases. In two of these the lesions persisted for several months after stopping solganol B, and were followed later by glossitis of several months' duration. Conjunctivitis occurred in three cases; in one there was an associated facial edema. A "metallic taste" was noted by one patient and bronchial irritation (gold bronchitis) by two.

Albuminuria. Minute amounts of albumin were found in the urine at some time or other during the course of therapy in approximately one half of the patients. There was no other evidence of renal irritation or damage in these cases. Significant amounts of albumin, however, were found in the urines of four patients. In all of these there was clinical evidence of nephrosis. In one the albuminuria developed during the early part of the second course of gold sodium thiomalate and disappeared completely nine months after its first appearance. In another patient the albuminuria is still present although there is no blood pressure elevation, edema or azotemia; the serum proteins are low. A third patient with albuminuria had an advanced rheumatoid arthritis and marked avitaminosis. He received 18 injections of myochrysine and returned approximately one year later with albuminuria, hypoproteinemia and a reversal of the albumin globulin ratio; the urinary sediment and blood urea were normal. This patient subsequently died, and at autopsy the kidneys showed amyloid disease. Microscopic studies were not made. In the fourth patient, the albuminuria occurred after two courses of gold and was associated with granular casts in the urine, peripheral edema, hypoproteinemia, normal blood urea, normal kidney function tests and a normal blood pressure. The albuminuria disappeared completely and recurred two years later following the development of fatal streptococcal endocarditis with septicemia. At autopsy the kidneys showed chronic pyelonephritis and amyloidosis.

Blood Changes. Anemia. Some degree of secondary anemia was present in most patients before the institution of chrysotherapy. When this was extensive correction with transfusions and other anti-anemia medication preceded the administration of gold. Following the use of large doses of gold the anemia became more marked in most cases. On the contrary, when small doses were used, a definite improvement in the blood picture resulted. Although most of the patients with an anemia received iron simultaneously, this improvement with small doses of gold was also noted in the absence of any anti-anemic medication in many instances. We are unable at present definitely to explain this effect of gold. It may act as a stimulant to the hematopoietic system of the body; when iron is also used, it may exercise a catalytic action not unlike that attributed to copper.

Eosinophilia. Eosinophilia exceeding 5 per cent was found in 11 cases; in five of these it exceeded 10 per cent. One patient developed an eosinophilia of 90 per cent with an associated rash and delirium following the fifth

injection of gold (500 mg.). Bone marrow studies in this case also revealed a marked eosinophilia. In a second case the eosinophilia was accompanied by granulocytopenia and a cutaneous eruption. Skin or mucous membrane lesions were found associated in four additional cases manifesting eosinophilia. In the remaining patients, no other associated toxic manifestations were noted. We were unable to substantiate the observation made by Sundalin that a high eosinophilia was always associated with a low sedimentation rate.

Agranulocytosis. This condition was observed in one case of our series. It occurred after the administration of only 300 mg. of gold, and was associated with a rash. The granulocytopenia persisted intermittently for five months with ultimate recovery. This patient had an allergic diathesis with a sensitivity to such drugs as aspirin.

Thrombocytopenia. Thrombocytopenia developed in three patients, one of whom died. In the latter an extensive subdural hematoma and multiple petechial hemorrhages were found throughout the body at autopsy.* In the second case of purpura a thrombocytopenia (19,300 platelets), high fever, joint swelling and a monocytosis (22 per cent) followed the administration of 500 mg. of gold sodium thiomalate. The latter was discontinued, and after the subsidence of the acute reaction the platelet count returned to normal and there was a complete restoration of the joints to normal. The third patient developed purpura with a moderate thrombopenia at the end of the second course of gold sodium thiomalate (1800 mg.), although a similar amount of gold given in the first course did not result in either of these toxic effects. After withdrawal of the drug, the purpura subsided and the platelet count returned to normal. Two years later, gold therapy in small doses (10 mg. twice weekly) was resumed, and after the eighth injection the platelet count dropped to 74,300 without purpuric manifestations. This promptly returned to normal after therapy was discontinued. One month later large doses of vitamin K (synkamin) were started in an attempt to prepare the patient against further thrombopenia. After four months, small doses of gold (10 mg.) were again resumed and were given in conjunction with synkamin. At the present writing, no further thrombocytopenia has developed.

MISCELLANEOUS REACTIONS

Diarrhea and abdominal cramps were experienced by 10 patients. In none of these was there evidence of bleeding. Jaundice was never observed. In rare instances, a sense of precordial discomfort was experienced following the injections, and in one patient a true anaphylactic reaction with stenocardia and marked anxiety developed immediately after the intramuscular administration of only 25 mg. of gold sodium thiomalate. The subsequent injec-

---

* This was one of the first patients treated by us. The significance of the purpura unfortunately was not recognized and the drug was not immediately discontinued.

tion of very small and gradually increasing doses in this case resulted in marked clinical improvement without further reaction.

A few patients experienced temporary increase in joint pains and stiffness. In two instances, transitory blurring of vision was noted. The so-called "nitritoid" reactions, characterized by vertigo, giddiness, flushing of the face and headache, were observed in varying degrees in most patients treated during the year 1940. Since these reactions are now observed very infrequently, it is assumed that they were related to the quality of the product available at that time.

RESULTS

The results in the present series are recorded in table 1. The *mild cases* all received at least one course of gold, five receiving two or more courses.

TABLE I

Severity of Arthritis	Total No. Cases	Initial Result			Relapses	Follow-Up Study			Rehabili-tated
		Imp.	Question-able Imp.	No. Imp.		Permanent Imp.	No. Imp.	No Follow-Up	
Mild......	14	13	0	1	3	11	1	2	4
Moderate .	30	24	4	2	11	18	8	4	11
Severe....	57	23	8	26	17	13	30	14	7

Improvement was noted in all symptoms, notably pain and stiffness, in all but one of these cases (93 per cent). An improvement in the general well-being of the patients was also observed. The only bedfast patient in the group became ambulatory. Relapse after the first course occurred in three patients. In one of these a second course was given with a resulting prompt remission of the symptoms.

A follow-up study was made on all but two of the mild group (table 2). The original improvement noted was found to persist in all at this follow-

TABLE II

FOLLOW-UP STUDY

Distribution According to Interval after Treatment

Time Interval after Treatment	Mild	Moderate	Severe	Total Cases
1 yr.	8	14	6	28
2 yr.	1	3	6	10
3 yr. or more	3	9	31	43
No follow-up	2	4	14	20
Total	14	30	57	101

up examination. The four patients who were formerly incapacitated had returned to work. The status of the remainder was unchanged. Since only one year has elapsed since the termination of therapy final conclusions concerning the value of gold treatment in this group cannot be drawn.

In those classified as *moderately advanced,* one-third had more than one course of injections.   Eighty per cent of the entire group experienced improvement following one or more courses.   In four other patients the improvement was only slight or questionable, and in two no benefit was noted. All eight patients who were bedfast became ambulatory.   Three of the four patients who required a cane were able to discard this support after completing therapy.   Relapses occurred in 11 of the patients who had originally improved.   Of the latter, eight had remissions following a subsequent course. The remaining three failed to have a remission.

A follow-up study was possible in all but four of this group.   Of all cases originally showing definite improvement 78 per cent continued to show this improvement at the time of the check-up examination.   No patients became worse.   Eleven returned to a gainful occupation after having been previously incapacitated.   Ten who had never been incapacitated, continued with their usual activities after receiving treatment.   The remaining patients, although showing definite improvement, had not returned to active work at the time of the follow-up study.   Since the final observation was made after only 12 months of therapy in only half of these patients, we consider it premature to draw final conclusions regarding the efficacy of gold therapy in this group.

In the *severe* advanced cases definite improvement was observed following one or more courses in 23 cases (40 per cent), whereas in eight the improvement was only slight or questionable.   Twelve of those who were improved had previously been bed-ridden.   In the remaining group (45 per cent) no improvement was noted at any time.   Relapses occurred in 90 per cent of all cases that had previously showed some degree of improvement.*   Nine of the latter have since had remissions following subsequent courses whereas eight have failed to improve.   Although some in the far advanced group noted an alleviation of joint pain, the principal improvement experienced was that of increased joint mobility.

A follow-up study was made in all but 14 of this group, three of whom had died.   The original improvement noted was found to persist in 13 (56 per cent) of those who had experienced definite improvement after completing treatment.   Two patients, neither of whom had ever noted a marked improvement, were definitely worse at the time of the follow-up study. Seven patients (12 per cent) were totally incapacitated by their illness.   Two of these later had a relapse which again temporarily incapacitated them. None of the other advanced cases was able to return to active work while under our observation.   Since the follow-up studies in this advanced group were made after an interval of more than two years in most of the patients, the observed effects of therapy are considered to have real significance.

Combining all three groups of patients, there was noted a definite improvement in 60 per cent.   This figure checks closely with the improvement rate of 66 per cent of Hartfall et al.,[6] 70 per cent of Forestier,[7] 66 per cent

* In four cases information relative to relapses was not available.

of Cecil et al.[4] and 61 per cent of Smyth and Freyberg.[8] Twenty-nine per cent of our cases showed no improvement at any time. Two patients became definitely worse. Twenty-one patients were released from bed confinement; 22 who were incapacitated returned to work.

Relapses occurred in 55 per cent of all cases showing an initial improvement. We are in agreement with Cecil that most relapses come on two to three months after cessation of therapy. For this reason we believe that careful and frequent observation following the cessation of therapy is important in order that relapses may be avoided or checked in their incipiency by another course of gold. It has not been our experience that relapses are usually milder than the original attack as reported by Cecil.

COMMENT

A satisfactory evaluation of any form of treatment for rheumatoid arthritis is admittedly difficult. The variable course of the disease with its natural tendency to spontaneous remissions makes hasty conclusions regarding the effectiveness of any therapeutic agent inadvisable. Thus, in a recent publication Short[9] recorded that 53 per cent of a series of 300 arthritic patients treated in the Massachusetts General Hospital during the past ten years experienced more or less satisfactory improvement after receiving nothing but "general therapy." Because of the danger of relapse, the calculation of results immediately after the completion of therapy is inadvisable. It is well known to all who have observed arthritic patients that a reactivation of the process may occur in the joints of patients at any time, even after years of quiescence. Prolonged observation is, therefore, essential in order that permanency of results may be assured. The follow-up studies in this series were made to avoid premature conclusions regarding gold therapy.

Satisfactory means for measuring small degrees of improvement in arthritic patients are not available. We made numerous attempts to measure changes in joints by means of a goniometer, and to determine the strength of the patients' hands as an index of improvement, with a dynamometer. Although there was noted slight change in some of the patients, neither method proved sufficiently satisfactory to continue their use. Because of the lack of an adequate index of progress, comparison of results with those published elsewhere is difficult. It is necessary to distinguish between limited subjective improvement which frequently follows bed rest alone, and an unmistakable change in the condition of the patient resulting in complete rehabilitation. Between these two extremes are various degrees of improvement. Thus, there may result an increase of only 10 per cent flexion in a joint, enabling the patient to perform some simple, though important, function which was not previously possible. To the patient this is an unmistakable improvement, and should be so construed, and yet socially and economically the patient is no better. In like manner, the patient may become ambulatory as a result of improvement in the joints of the lower extremities, and yet be unable to earn

his own living because of advanced deformities in the upper extremities. The difficulty of evaluating progress is obvious. The *ideal* criterion for recovery would seem to be the complete restoration to social and economic independence rather than the simple relief of symptoms in any one joint.

The sedimentation rate has been used by most clinicians as an index to the severity of the disease and as a criterion of improvement. Although it reflects the clinical course in many cases, we are at present unable to share the enthusiasm of many concerning the value of this test. Thus, we have observed patients with clinically active arthritis whose sedimentation rate was within normal limits. In other cases there has been a complete subsidence of the acute process for many weeks during which time the sedimentation rate remained persistently elevated. We have not used the sedimentation rate as a criterion for a continuation of gold therapy as recommended by Forestier.[10]

The classification of our patients according to the extent of the arthritic process was considered necessary in order to give a fair estimation of the effect of the drug. Failure to do this in some of the series recorded in the literature undoubtedly accounts for much of the variation in the improvement rates found. Series made up predominantly of early cases with little or no joint destruction would be expected to have higher improvement rates than those comprised largely of bedfast or wheel chair patients in an institution. The unusually good results recorded in the mild cases of this series, and the much less satisfactory results among our advanced cases illustrate this fact. Despite the low incidence of rehabilitation in the latter group we are still of the opinion that gold therapy is worthy of a trial in these human derelicts. In spite of their incapacitation, relief from pain and stiffness is very gratifying to them.

We agree with the observations made by Smyth and Freyberg [8] that the clinical results are just as satisfactory with small doses of gold (50 mg. weekly) as those obtained with larger ones. If this is true, there would seem to be no justification for using the latter.

The potential toxicity of gold compounds makes their indiscriminate use unwise and dangerous. Careful observation for early indications of toxic effects is essential, and when the necessary clinical and laboratory observations cannot be made, gold should not be used. The pathogenesis of these reactions is not known, but their occurrence after very small doses early in the course of treatment, in most cases, suggests a sensitivity reaction or an idiosyncrasy to the drug rather than a simple intoxication by a heavy metal. This theory has been advanced by others.[5, 11] The absence of toxic reactions in some of our patients who received as much as 5 to 9 grams of gold over a four to six year period further substantiates the former view. Thus, 19 of our patients received a total of from 5 to 9 grams of gold, and only six of these had a mild toxic reaction (rash) at some time during their therapy. In one additional case a mild diarrhea occurred. No *serious* complication was ever observed in this group of patients. We have at no time observed

normal sedimentation rates in patients with toxic reactions as reported by Ellman and Lawrence.[12]   Inasmuch as we have observed practically no toxic effects since using very small individual doses, we are forced to conclude either that the amount of gold given in each dose has some effect on the production of a sensitivity reaction in patients, or that we have been recently using a less toxic and more highly refined preparation.   We are inclined to favor the former view.   We are unable to agree with Sundalin[5] that large doses are no more toxic than small ones.

The exact mode of action of gold in arthritis is unknown.   Hartung and Cotter[13] have recently reported that serum from patients with atrophic arthritis becomes bactericidal against a strain of hemolytic streptococcus when treated with gold.   Since the rôle played by this organism in rheumatoid arthritis is now questionable the applicability of this theory to human arthritis is somewhat doubtful.   The development of rheumatic nodules *during* the course of gold therapy in six of our cases would indicate that chrysotherapy does not prevent the development of new rheumatic tissue.*   This evidence mitigates against the bacteriostatic theory of Hartung and Cotter.   Another explanation for the mechanism of the action of gold lies in its stimulating effect on the recticulo-endothelial system.   This theory has been advanced by Kling, Saskin and Spanbock.[14]   Evidence for this is not complete.   A third possible mode of action lies in its effect on the water metabolism of the body.   In recent studies by Jacobson, Leichtentritt and Lyons,[15] the effect of water loss from periarticular tissues was observed following diuresis by ammonium chloride and mercupurin.   A profound improvement in the joint symptomatology, i.e., pain, stiffness and swelling, was demonstrated.   It is suggested that gold in suitable combinations may produce a similar though less striking diuretic effect, with a resultant loss of tissue fluid and a consequent improvement in joint symptomatology.†

CONCLUSIONS

1. Gold is an effective remedy for the treatment of rheumatoid arthritis, aiding in the alleviation of all joint symptoms and effecting rehabilitation in a significant percentage of patients.

2. Aurotherapy should be limited to rheumatoid arthritis, and is most effective in the early stages of the disease.   It is also frequently effective in relieving pain and stiffness in advanced cases, and is therefore worthy of a trial in these patients.

3. Careful and repeated follow-up observations should be made before drawing final conclusions about this therapeutic agent, since there is a high incidence of relapse and remission in the natural course of. rheumatoid arthritis.

* A detailed report of these cases will be submitted for publication in the near future.
† Studies on the water metabolism of arthritic patients receiving gold therapy are now in progress at the Wm. J. Seymour Hospital.

4. Gold is a toxic drug and should be used only by those having experience with it. Careful observation for the early appearance of toxic effects should be made in all patients receiving this form of therapy.

5. The toxicity is probably the result of individual drug sensitivity rather than due simply to heavy metal intoxication. The administration of such large amounts of gold (7–9 gm.) as reported in this paper without the development of toxic reactions would tend to support this contention.

6. The exact mode of action of gold is not known. The observations herein recorded concerning the development of rheumatic nodules during its administration would seem to mitigate against the bacteriostatic theory advanced by Hartung and Cotter.

BIBLIOGRAPHY

1. LANDÉ, K.: Die günstigen Beeinflussung schleichender Dauerinfekte durch Solganol, München. med. Wchnschr., 1927, lxxiv, 1132–1134.
2. PICK, ERNST: Versuche einer Goldbehandlung des Rheumatismus, Wien. klin. Wchnschr., 1927, xl, 1175–1176.
3. FORESTIER, J.: L'aurothérapie dans les rheumatismes chroniques, Bull. et mém. Soc. méd. de hôp de Paris, 1929, i, 323–327.
4. CECIL, R. L., KAMMERER, W. H., and DePRUME, F. J.: Gold salts in the treatment of rheumatoid arthritis; a study of 245 Cases, ANN. INT. MED., 1942, xvi, 811–827.
5. SUNDALIN, F.: Die Goldbehandlung der chronischen Arthritis unter besonderer Berücksichtigung der Komplikationen, Acta med. Scandin., 1941, cxvii, supp., 1–291.
6. HARTFALL, S. J., GARLAND, H. G., and GOLDIE, W.: Gold treatment of arthritis, a review of 900 cases, Lancet, 1937, ii, 784, 838.
7. FORESTIER, J.: Rheumatoid arthritis and its treatment by gold salts, Lancet, 1934, ii, 646.
8. SMYTH, C. J., and FREYBERG, R. H.: Experiences with gold salts in the treatment of rheumatoid arthritis, Univ. Michigan Hosp. Bull., 1941, vii, 45–47.
9. SHORT, C. L.: Gold therapy of rheumatoid arthritis, Bull. New England Med. Center, 1942, iv, 31–34.
10. FORESTIER, J., CERTONCINY, and PERLES: La chrysothérapie prolongé dans les polyarthrites. Etude de cinquante cas, La révue du rheumatisme, 1936, iii, 485.
11. TZAUCK, A.: Bull. et mém. Soc. méd. d. hôp. de Paris, 1930, liv, 149, 228. (Quoted by Sundalin.)
12. ELLMAN, P., and LAWRENCE, J. S.: Gold therapy in rheumatoid arthritis; an assessment of its value with control experiments, Post-Grad. Med. Jr., 1938, xiv, 275.
13. HARTUNG, E. F., and COTTER, J.: The effect of gold sodium thiomalate administration on the bacteriostatic properties of the serum in patients with rheumatoid arthritis, Jr. Lab. and Clin. Med., 1941, xxvi, 1274–1284.
14. KLING, D. H., SASKIN, D., and SPANBOCK, J.: The mechanism of gold therapy in rheumatoid arthritis, Jr. Lab. and Clin. Med., 1939, xxiv, 1241.
15. JACOBSON, S. D., LEICHTENTRITT, B., and LYONS, R. H.: The effect of acid and alkaline salts on some patients with rheumatoid arthritis, Am. Jr. Med. Sci., 1942, cciv, 540.

SOME LEGAL ASPECTS OF HEART DISEASE AND THE ELECTROCARDIOGRAM *

By J. E. F. Riseman † and Hubert Winston Smith ‡,
Boston, Massachusetts

I. Nature and Volume of American Litigation Involving the Heart

THE advent of comparatively inexpensive portable electrocardiographic machines has greatly multiplied the number of tracings being made in the practice of medicine, and the uses and abuses now seen by cardiologists will be secondarily reflected in court proceedings. We intend in the present paper to consider some of the pervasive problems regarding the use, value and shortcomings of electrocardiograms as evidence.[1] As a preliminary step, it would seem wise to consider the nature and source of cardiac litigation, and certain legal principles which orientate the problem of proof.

Most cases which come before legal tribunals are terminated in the trial court, where no statistics are kept that enable one to compare the incidence of various types of law suits. Workmen's Compensation Commissions in the larger industrial states, however, for some years have been issuing statistical analyses of claims, and these often disclose valuable comparative information regarding mode of accident and nature of injury suffered.

A certain percentage of cases are carried on appeal to higher courts. Such cases are disposed of by decisions supported by written opinions, which are printed and preserved as precedents.

It is evident from a survey of appeal litigation that a continuing flow of cardiac cases is going through the courts. Most of these are workmen's compensation cases; most of them result from some lifting, straining, or unusual exertion in the course of work, rather than from direct trauma; and most of them are disasters suffered by persons already afflicted with heart disease. Careful study of Workmen's Compensation statistics leads to the inference that, even in this more active field, injuries to the heart constitute a very small fraction of total claims.

The following legal categories are the main ones which may be expected to give rise to cardiac litigation:

[1] How the electrocardiograph works is explained for the lawyer in Riseman, J. E. F., Principles of electrocardiography, 15 Rocky Mt. L. Rev. (April 1943) ——. The present paper is a specially adapted and more ambitious version of Smith, H. W., and Riseman, J. E. F., Applied use of the electrocardiogram in legal proceedings, 15 Rocky Mt. L. Rev. (April 1943) ——.

(1) *Tort law:* If A intentionally or negligently exposes B to an injurious stimulus causing cardiac injury or disability, this will afford grounds for liability in damages. The injured person may recover for medical, hospital and nursing expenses; for pain and suffering; for loss of earnings; and for any other items which the law allows in an effort to afford just compensation for the injury, including future as well as past effects.

Example: *Tort Case: Acute dilatation of heart in 11 year old boy allegedly caused by electric shock.*

B, an 11 year old boy, received a high voltage shock as a result of C Public Service Company's negligent failure to safeguard its lines from contact of children known habitually to play around and on one of the towers. In an action by B against C for negligent injury, B's doctor testified that "in all cases of severe electric shock there is a dilatation of the heart." He also testified that he had found, both by clinical examination and roentgen-ray pictures, that the plaintiff was so affected, and would be permanently. The jury returned a verdict in B's favor for $33,000. Affirmed on appeal.

Wolczek v. Public Service Co. of Northern Ill., 342 Ill. 482, 174 N.E. 577 (1931).

It is held generally that a plaintiff may recover damages for substantial aggravation of a preëxisting complaint, but not for that portion of the disability which existed before the accident and was not caused by it. It is obviously difficult for the medical man to estimate what portion of the final disability should be attributed to the accident and what portion to preëxisting disease or impairment. At present this segregation is not being carried out by all expert witnesses, and there is a regrettable tendency on the part of both counsel and witness to attribute the full disability to an accident, even though part of the complaints already existed.

(2) *Workmen's Compensation claims:* If employee A suffers injury from an *accident* arising out of and in the course of employment, and his employer carries workmen's compensation insurance, A is entitled to receive such benefits without proving any negligence or fault. The medical man must realize that the workman cannot recover if he is unable to prove the occurrence of an "accident." This involves application of legal interpretation to facts presented by testimony. As in all civil litigation, one who seeks to prove a necessary fact must establish it by a preponderance of the substantial evidence. It must appear that the accident was a *probable* substantial cause of the disability. No award can be entered if at the end of the hearing it appears from all the evidence that the proof of causal connection is conjectural. Testimony that the accident "might" or "could" have been the cause is too conjectural, standing alone, to prove causation. The fact that an accident could have caused an injury does not prove that it did, but the better court decisions hold it is competent as evidence of "probable" causation, if coupled with other evidence excluding the operation of all other possible causes capable of producing the injury.

Doctor's rôle in proof-making: The doctor's province as a prospective expert witness is to examine the claimant and determine the following facts:

(a) Is A suffering from a cardiac disability, and if so, does it involve partial or total incapacity, and is it temporary or permanent in character? ·

(b) Considering the history of the alleged accident, was the stimulus described adequate to cause the cardiac injury? Is such a mechanism of injury recognized scientifically—i.e., is there scientific warrant, in light of medical facts now known, for giving a professional opinion that the described stimulus *could* cause the alleged result?

(c) Considering the described stimulus, the symptomatology and the medical findings, and eliminating other possible causes by the orthodox differential methods required by good medical practice, can the expert give a professional opinion (perhaps based on a hypothetical question gathering together all relevant data) that the described stimulus probably *did* cause the described disability? A particular medical witness is entitled to give a "might" or "could" opinion as proof that such a sequence is scientifically possible, but the *plaintiff* will need to tender other evidence that the accident was a probable substantial cause without which the injury would not have occurred.

Failure of commissions to partition disability between accident and pre-existing causes: Here again, there is not a very scientific handling by commissions or courts of the partitioning of disability between accident and pre-existing causes. This opens up a realm of legal discussion and of social policy too broad for treatment in this paper.[2] It must suffice to say that most commissions and courts take the view that the employer accepts the idiosyncratic or impaired employee as he is, and if the latter becomes disabled by virtue of an accident which would not have injured the average person, the disability is nonetheless compensable. So long as this principle of compensation prevails, the doctor will be required to say whether the accidental stimulus or trauma was a probable substantial cause of a lesion appearing for the first time or of the aggravation of a preëxisting lesion, and to what extent the workman is and will be disabled.

Workmen's compensation claimant must prove an "accident," but this term is liberally construed so that extraordinary physical stress or strain, or nervous shock, not normally incident to the employment, is considered to be an "accidental" cause of any resultant injury.

Cardiac disasters which occur in industry usually befall workmen already subject to heart disease. To establish a compensable claim they must necessarily prove that the condition was substantially accelerated or aggravated by an accident arising out of and in the course of employment. If the employed workman suffers cardiac damage while performing ordinary tasks involving no more than usual stress and strain, the claim for compensation will fail for inability to prove "accidental injury."

[2] Regarding the proper measure of an actor's legal duty to idiosyncratic or hypersensitive individuals, see Solomon, H. C., and Smith, H. W.: Traumatic neuroses in court, Am. Jr. Psychiat., 1943, xcix (Sept.–Oct.); also, Cobb, S., and Smith, H. W.: Relation of emotions to injury and disease: A call for forensic psychosomatic medicine, ANN. INT. MED., 1943, xviii (Aug.).

Example 1: Blacksmith with chronic myocarditis suffered fatal coronary occlusion while shoeing horse; held (3–2 decision), reversing Board's award of compensation, that proof was lacking of sudden or extreme exertion and hence the injury was not "accidental."

La Fountain v. La Fountain, 21 N.Y.S.(2d) 193, 259 App. Div. 1095 (1940).

Example 2: A 58 year old warehouse laborer, who had long suffered from coronary sclerosis, was performing his accustomed task of pushing a truck over a slight elevation when he suffered a heart attack which totally and permanently disabled him. Held, vacating award of compensation and reversing Board and lower courts: The injury occurred in the normal performance of employment and there was no "accident."

Crispin v. Leedom & Worrall Co., 341 Pa. 325, 19 A.(2d) 400 (1941).

Example 3: Fireman suffering from preëxisting heart disease fought a fire in smoke and fumes for three hours and subsequently developed coronary thrombosis; held, vacating award of compensation and reversing Board and lower courts: Aside from question of causation, fighting fire is an ordinary incident of a fireman's employment, and the claim for compensation must fail for want of any "accident."

Brown v. City of Omaha, 141 Neb. 587, 4 N.W.(2d) 564 (1942).

Example 4: Where 56 year old laundry engineer suffering from preëxisting heart disease, collapsed from coronary occlusion, after painting boiler, held: Lack of any "accident" makes the injury noncompensable.

Siscoe v. Cooley (La.App.), 9 So.(2d) 313 (1942).

The courts hold that if the heart disability is due to some unusual exertion, strain, or lifting which is foreign to the normal work done in that type of employment, the effort is extraordinary and so may be treated as an "accidental injury," even though the exertion itself was intentionally made. This reflects perhaps somewhat of an extension of the concept of accident, but liberal construction of the compensation laws has resulted in these "overexertion" cases being treated in the same way as accidental falls or other unexpected mishaps.

Example 1: Carpenter with preëxisting heart disease collapsed and died after unusual exertions, on a very hot day, in carrying heavy pieces of lumber a block and a half, then up to a scaffold 18 or 20 feet above the ground. Held: A compensable accident.

Schneider v. Haerter, 119 N.J.Law, 548, 197 A. 281 (1938).

Example 2: Collapse and death of workman suffering from preëxisting heart disease, was a compensable "accident" where episode followed muscular exertion in using a heavy sledge hammer rather than the customary pick and shovel.

Bergagna v. Dept. of Labor and Industries, 193 Wash. 263, 91 P.(2d) 551 (1939).

Example 3: Fireman, who had preëxisting heart disease, sustained injury from carrying at one time three 27 pound tarpaulins up four flights of a burning hotel. Held: The injury was a compensable "accident" as the exertion was much greater than the usual or customary strains characteristic of his employment.

Brown v. Minneapolis Board of Fire Underwriters, 210 Minn. 529, 299 N.W. 14 (1941).

Example 4: Excessive exertion by 68 year old policeman in effecting arrest caused his death from preëxisting myocarditis; held: A compensable "accident."

Green v. City of Bennettsville, 197 S.C. 313, 15 S.E.(2d) 334 (1941).

Example 5: Sixty-three year old janitor, not shown to have been subject to preëxisting cardiac disease, died suddenly from acute dilation of heart following unusual

exertion from extra work and longer hours moving furniture and stoking furnace in preparation for an entertainment. Held: A compensable "accident."

Fittro v. Industrial Commission, 377 Ill. 532, 37 N.E.(2d) 161 (1941).

(3) *War risk insurance:* The veteran must prove that he suffered a service-connected total and permanent disability before his policy lapsed for non-payment of premiums. It is not enough that he then had a partial disability which later became total and permanent. The courts do hold, however, that medical history subsequent to lapse of the policy is admissible evidence to show that in fact the assured was actually totally and permanently disabled when the policy lapsed. This is very helpful in psychiatric conditions where early stages of schizophrenia may be mistaken for a transient neurosis. Cardiac cases were comparatively infrequent in the war risk series after the last war, and because of careful screening by pre-induction medical examinations, they will probably be relatively infrequent after the present war.

(4) *Life, health and accident insurance:* If the assured, before applying for his policy, was suffering from heart disease and knowingly concealed this fact, the insurer may cancel the policy on the ground of breach of warranty or fraud, tendering back any premiums already paid. If the heart disease develops subsequent to the date of taking out the policy, from any cause whatsoever, the assured will be entitled to payment of benefits as provided by the terms of the policy. Here the main question which will arise for medical consideration will be whether the assured actually has heart disease, and whether it prevents his earning a living.[3] In this connection the doctor obviously must take into account the nature of the work for which the assured has training and experience, and on the basis of gainful employment thus open to the individual, say whether his cardiac condition will permit his working full or part time, or whether he has become totally and permanently disabled.

Many policies carry double indemnity provisions in case death occurs as a result of accidental means exclusive of disease. In such cases (in contrast to Workmen's Compensation cases), the accidental injury must have been the *sole* cause of the disability or death, and if preexisting disease is a contribu-

[3] In 1937, a number of lawyers, doctors and laymen were brought to trial in the Federal district court of New York City for participating in a giant conspiracy to obtain payments on disability insurance by feigning heart disease. The *modus operandi* was quite interesting. Financially embarrassed policy holders, located and secured as clients by "runners," were coached by doctors and lawyers in the symptoms of heart disorder (particularly *angina pectoris* and *coronary thrombosis*), so that they could give impressive histories to unsuspecting general physicians. Some policy holders would simulate cardiac collapse in public places in order to be sent to hospital. Oftentimes the medical record was built up further prior to making claim by sending the coöperative policy holder for an electrocardiogram immediately after his heart action had been deranged by administering digitalis or other drugs. This scheme succeeded for several years, involved life policies amounting to more than ten million dollars in forty different companies, and resulted in payments and cash settlements of several hundred thousand dollars, before the conspirators became incriminated through increasing boldness and recklessness.

Hedley, O. F.: The fraudulent use of digitalis to simulate heart disease, ANN. INT. MED., 1943, xviii, 154.

tory cause the case falls outside the risk insured. If it can be shown that a preëxisting disease had become dormant but was excited into activity by the accident, most courts hold the accident to be the efficient cause of the disability and allow recovery of benefits. Many persons have been able to recover under accident insurance policies on this theory of arrested, or inactive preëxisting disease, exacerbated by accidental injury, and it makes no difference that the effect of the previous pathological process was to leave a weakened constitution more vulnerable to trauma.

Example 1: *Accident insurance: No recovery of benefits possible where preëxisting disease was a substantial cause of death; electrocardiograms used to prove progressive preëxisting disease.*

Action for death of an insured fireman, under an accident insurance policy which provided for payment of $2,000 to the beneficiary when the member "shall through external, violent and accidental means receive bodily injuries which shall independently of all other causes result . . . in the death of the member."

A 46 year old fireman was hospitalized on April 23, 1936, following a severe attack of angina pectoris. He drew disability benefits until June 24, 1936, when he returned to work, and electrocardiograms showed coronary thrombosis. On November 1, 1936, after lifting a ladder at a fire and lowering it to get under obstructing wires, he left the fire and was presently found dead on the running board of the fire truck. A jury found the death was accidental and returned a verdict for $2,000 in favor of the beneficiary of the accident policy. Medical evidence, including autopsy, showed that the assured died of angina pectoris, "a progressive and permanent disease in which attacks are provoked by emotion, excitement or physical exertion."

Held, on appeal: There could be no recovery for accidental death, for the angina pectoris was at least a concurring cause of the death.

Schroeder v. Police and Firemen's Ins. Ass'n, 300 Ill. App. 375, 21 N.E.(2d) 16 (1939).

Example 2: *Accident insurance: Strenuous efforts in loading wild horse, leading to symptoms of coronary thrombosis, from which assured had not previously suffered, was the accidental and sole cause of the subsequent death.*

X, an apparently healthy 50 year old employee of a land company, on July 23, 1938, undertook to load a wild horse into a truck. He worked and struggled with the horse for about two hours, and at times was dragged around by the horse. The exertion was so strenuous that X, the insured, was completely exhausted at the end of the struggle, complained of being tired, and when he went home declared that he was sick and went to bed. X had no supper that evening and he complained of pain in the region of the heart and in his left arm. He was nauseated and troubled with shortness of breath and sleeplessness. He remained in bed the next day, and thereafter was up and about, but unable to undertake any substantial work, and on August 16, 1938, he died of coronary thrombosis which doctors imputed to the tussle with the horse.

The beneficiary of an accident insurance policy carried by X sought to recover death benefits of $2,000 payable "If the Insured shall through accidental means, sustain bodily injuries as described in the Insuring Clause, which shall, independently and exclusively of disease, and all other causes, immediately, continuously and wholly disable the Insured from the date of the accident and result in death within 13 weeks."

Verdict and judgment for P for $2,000. Held, on appeal: Affirmed.

Jacobson v. Mutual Ben. Health & Accident Ass'n, 70 N.D. 566, 296 N.W. 545 (1941).

II. NATURE OF THE STIMULUS AND PROOF OF CAUSE-EFFECT RELATIONSHIP

It is an aid to the development of criteria in Scientific Proof, and conducive to better thinking, if we analyze cause-effect relationships in terms of mechanisms of injury. One phase of this process is to classify stimuli. The alleged injurious stimuli relied upon in legal claims for cardiac disability fall into four main groups:

(1) Direct trauma to the heart, including heavy impact injuries to the overlying thorax.

(2) Indirect trauma due to excessive demands made upon an impaired heart, usually consisting of some extraordinary lifting or straining, which could not be regarded as a normal task in that line of employment. This group includes, also, peripheral trauma at a locus so far removed from the heart that any effects on that organ are secondary.

(3) Exposure of the heart to noxious agents carried in the blood stream, such as carbon monoxide or other poisons.

(4) Injuries ascribed to what we may call psychosomatic stimuli, consisting of nervous shock without substantial impact, or of emotional upset, or of other psychic disturbances.

Effect of immediacy of cardiac injury on problem of proof; use of electrocardiograms as "completion evidence" to clarify existence of cause-effect relationship where stimulus is far removed in time from alleged consequential injury to heart:

Inspection of the law cases shows that a goodly portion of cardiac claims involve some specific stress or strain out of the ordinary, followed by speedy collapse of the workman. If the subject dies within seconds or minutes thereafter, the cause-effect relationship is more easily established. Time does not permit the making of electrocardiograms and the need for their use is not so pressing.

If, on the other hand, the collapse at work is followed by a period of weeks or months before the appearance of the final injury imputed to the stimulus, very serious problems of proof arise. In the first place, one who is subject to preexisting heart disease has independent grounds for suffering injury, for cardiac decompensation may occur, particularly in far advanced cases, as a result of extraneous circumstances and even spontaneously. This time gap between stimulus and alleged response more than once has caused courts to deny compensation on the ground that proof of causation was speculative or conjectural.[4] It is in these cases where a long time interval

[4] Hawkins v. Powels Tillery Steam Co., Ltd. (Eng. 1911), 1 K.B. 988, 4 B.W.C.C. 178. (X, a 62 year old colliery worker, became sick at work ten minutes after finishing moderate exertions in pushing empty tramcars and died that night of angina pectoris. Held, vacating award: Since the medical evidence showed that angina pectoris attacks may be provoked by several causes, and the·claimant did not rebut the possible operation of these, the proof of causation was too conjectural to permit a recovery of benefits. Timely electrocardiograms, made immediately after symptoms appeared, would have helped to resolve this ambiguity of causation.)

elapses between stimulus and alleged response that the electrocardiogram can render signal aid in many cases by providing what we call "completion evidence." By this we mean that the electrocardiogram may produce objective evidence immediately after the collapse and at intervals thereafter which will be of value in helping to prove or disprove the fact and continuity of causation. This application of the electrocardiogram involves the supplying of "bridging evidence" to fill in what may be a silent or ambiguous period between collapse at work and a subsequent final cardiac damage far removed in point of time.[5] It would therefore seem wise that all workmen who collapse in the course of their employment be hospitalized, and that initial and interval electrocardiograms be made. This can be done without risk of injury to the sick workman. These post-accident records are properly admissible in evidence, even though there be no pre-traumatic electrocardiograms for comparison. The post-accident electrocardiograms, in cases where they have any probative value at all (see table 1), constitute some circumstantial evidence, taken in conjunction with other examinations and findings, of the presence or absence of heart disorder. Clearly the strength of the electrocardiogram evidence is increased if pre-accident electrocardiograms are available to show condition of the heart prior to the alleged injury. Every workman who is to be employed for heavy labor should have such an electrocardiographic tracing made as a part of the medical examination at the time he is hired. This would involve no great expense and would serve to secure justice to both employer and employee. It may be that labor unions will need to espouse the systematic taking of electrocardiographic tracings · in hospitals following collapse at work.

The physician as expert witness: Opinions based on personal knowledge of case and opinions based on hypothetical questions:

In the usual medico-legal case, the physician will be asked whether the described stimulus, in light of all available facts, was a probable substantial cause of cardiac disability or symptoms. He may also be asked to appraise the disability in terms of its restrictive effect on occupational and personal pursuits, and to give a prognosis as well as diagnosis.

The physician must approach his task of explaining and elucidating these problems with a realization of the grave responsibility which is his. He must refrain from testifying if he feels the subject is beyond his professional attainments; he must take properly into account the opinions held by leading cardiologists; he must avoid the naive error of assuming that disability

---

[5] This "completion use" of the electrocardiogram is strikingly illustrated in Brown v. City of Omaha, 141 Neb. 587, 4 N.W.(2d) 564 (1942). Plaintiff, a fireman, afflicted with preëxisting heart disease, filed claim for total and permanent disability. He alleged that his disabling coronary occlusion or thrombosis was an accidental injury received in fighting a basement fire for three hours on September 28, 1939, in the midst of dense smoke and fumes. Electrocardiograms made thereafter and up through November 29, 1939, showed that P had not yet developed coronary thrombosis. An electrocardiogram made on November 30 and December 1, 1939, furnished conclusive evidence of disabling coronary thrombosis. In view of this evidence, the Supreme Court of Nebraska held that the fire-fighting clearly was not a cause of the thrombosis and vacated an award made by the Board and affirmed by the lower court.

which follows an accident is necessarily caused by it; and he must present his findings and opinions in a simple, clear way understandable by a court and jury not likely to be accustomed to medical terms.[6]

Physicians testify as experts in two possible ways. If they have gained first hand knowledge of the facts of the case, the attorney will use the direct question and answer method to elicit this information and any final opinions deduced from it. It may happen that the expert has never seen or examined the subject whose grievance is the basis of litigation. In that event all material facts supported by competent testimony of others may be summarized in a hypothetical question addressed to the expert to evoke his expert opinion. If the doctor has been called to *treat* the patient, courts in most American states will permit him to relate symptoms which the patient described, even though such utterances of a third person fall within the technical definition of hearsay evidence. If, however, the doctor was called in only to examine the patient for purposes of testifying in court, most courts refuse to let the medical man testify as to the symptoms related by the claimant. This difficulty is not insurmountable; it can be met by the lawyer's putting the patient on the witness stand and having him relate his symptoms, and then incorporating the symptoms in a hypothetical question addressed to the doctor. This device makes it clear to the jury that the doctor has had to accept the patient's honesty in relating the symptoms, and that, in so far as history goes, he is adopting the statements of the patient.

III. ADMISSIBILITY OF ELECTROCARDIOGRAMS AS EVIDENCE IN COURT

(1) *Physician who proposes to give an interpretation of an electrocardiogram must have his expert qualifications established to satisfaction of the court on preliminary or so-called "voir dire" examination.*

Since electrocardiographic tracings are not self-explanatory, but assume meaning only in connection with expert interpretation, they should not be allowed in evidence, nor should they be exhibited to the jury, without simultaneous proffer of a competent expert to explain their meaning and significance in relation to an issue in the case.[7]

If a lawyer proposes to use any witness as an expert, he must first establish his qualifications to speak on the proposed subject. This he will do by asking preliminary questions designed to satisfy the court that the witness by virtue of professional training, experience and familiarity with the literature of his subject, has acquired special knowledge and competency not possessed by the layman. The attorney will quickly interrogate the wit-

---

[6] One pressing need in medico-legal work is to avoid ambiguous terms; in the cardiac field this would include such ill defined diagnoses as endocarditis, myocarditis and acute dilatation. Courts should require pleadings to use accurate, specific terminology, for which see Nomenclature and Criteria for Diagnosis of Diseases of the Heart, 1940 (4th ed.), Am. Heart Assoc., N. Y.

[7] In Call v. City of Burley, 57 Ida. 58, 62 P(2d) 101 (1936), a personal injury case, a verified roentgenogram of plaintiff's pelvis was tendered without offer of any interpretation, and the court excluded it on the ground that "the average layman would get no information . . . unless the alleged fracture is pointed out and explained to him."

ness on such facts as his education, specialized training, experience, hospital affiliations and current practice. The general intent is not only to qualify the witness but to give him as much prestige and authority as his background deserves, and for that reason counsel usually goes further to inquire about important connections with learned societies, teaching and research activities, and particularly certification by specialized boards.

The lawyer for the opposing party has a right to cross-examine the witness to the end of showing that in fact he is not competent to appear as an expert witness. At the conclusion of the direct and cross-examination, the court will rule whether the witness is qualified as an expert or not, but this ruling may be reversed if during the course of trial it appears to the judge that the witness is in fact not qualified to give opinions on the subject in question.

It would be very helpful to courts in determining whether witnesses are qualified as experts, if the medical profession would devise some system of certifying what topics the given practitioner is competent to speak on by virtue of his attainments and field of concentration. This need is particularly keen in a field such as electrocardiography, where it is dangerous to lay down categorical norms of interpretation and much abuse may creep in if unqualified persons are allowed to rest extravagant opinions on particular tracings.[8]

[8] In future, many doubtful medico-legal claims involving the heart may be made on the basis of uncritical and extravagant use of the electrocardiogram if loose practices now current in the medical use of this diagnostic aid continue unabated. See Marvin, H. M.: Use and abuse of the electrocardiogram in medical practice, New England Jr. Med., 1942, ccxxvi, 213–217. The author comments on the unquestioned value of electrocardiography in such conditions as irregularities of cardiac rhythm, involvement of the heart during the course of systemic diseases, acute myocardial infarction, digitalis intoxication, structural lesions and the various types of cardiac neuroses. He feels, however, that much harm is being done, in the new widespread use of the electrocardiogram, largely as a result of the general practitioner's failure to recognize the following limitations on its value:

(1) Changes in the ventricular complex, including its terminal portion, have no special significance, with the exception of changes associated with myocardial infarction;
(2) The electrocardiogram hardly ever gives helpful information on the functional state of the heart, so that therapeutic questions of the amount of rest and action, and of the quantity of digitalis proper for the patient cannot be decided by the electrocardiogram;
(3) It is usually impossible to secure information about the prognosis from the electrocardiogram;
(4) The graphic records must be interpreted in light of clinical evidence;
(5) Many physicians are making unjustified diagnoses of heart disease solely on strength of minor variations in the electrocardiographic curves; these should never be accepted in absence of supporting clinical evidence;
(6) Misuse of the electrocardiogram is prevalent throughout the country;
(7) The American Heart Association has received a flood of letters from leaders in the cardiovascular field, asking for some board to establish certification of those physicians who are competent to interpret electrocardiograms. The primary intent would be to curb the present misuse of the electrocardiogram in the practice of medicine itself.

See, also, Willius, F. A.: A talk on certain prevailing fallacies in the application of clinical electrocardiography, Proc. Staff Meet., Mayo Clin., 1942, xvii, 137–140. The author attributes some of the main vices to:

(1) Naive assumption that fixed norms of interpretation can be employed automatically;
(2) Divorcement of electrocardiographic interpretation from clinical examination, re-

(2) Predicate which proponent must lay in order to have electrocardiograms received in evidence.

Whenever any special type of evidence is to be offered in court, certain preliminary steps must be taken to show that the apparatus and technic were adequate and trustworthy, and that the results tendered truly state the facts of the particular transaction.   This is very important because errors, negligent or intentional, may creep in at many successive points in the acquisition of evidence, and it would be an imposition on courts if one who sought to use a species of evidence were not willing to vouch for its reliability.

In this process of "laying the predicate," the physician will be called upon to testify:

1. That the electrocardiograph machine was standard and adequate equipment in good working condition, and properly standardized.[9]

2. That the electrodes and leads (Leads I, II, III, IV) were applied in the conventional manner and that the usually accepted technics were used in procuring the tracing.

3. That the electrocardiographic tracings were made by the physician himself, or that they were made under his personal supervision and direction by a competent technician, and that he is willing to vouch for their accuracy.[10]

4. That the tracings were made on a sitting or recumbent patient whose heart action was not then affected by any exertion or drugs.   The witness must be ready to affirm under oath that the electrocardiographic tracings are

sulting in errors of omission and commission since the electrocardiogram alone is not an adequate form of cardiac study;

(3) Failure of medical schools to provide adequate instruction in electrocardiography.

It goes without saying that this prevalent and growing misuse of the electrocardiogram is certain to be secondarily manifested in the courts of the land.   The only safeguard is for courts to hold to the strictest standards of competency in testing a doctor's fitness to give an expert opinion or interpretation based on the electrocardiogram.   Here signal help could be had from a "proficiency certificate" issued by the medical profession to those who propose to appear as electrocardiographic experts in legal proceedings.   See Smith, H. W.: Scientific proof and relations of law and medicine, ANN. INT. MED., 1943, xviii, 450–491; Clinics, 1943, i, 1404.

[9] When the electrocardiograph is properly standardized, a current of one millivolt will cause a deflection of the beam of the string shadow equal to one centimeter.

[10] If the technician is available, ordinarily he should be called to court, unless counsel stipulate in advance that the electrocardiograms to be used have been properly made and may be offered in evidence by agreement without formality of laying a predicate.   The technician should be charged with the duty of filling out a standard record each time an electrocardiogram is made and this should show the name and address of the patient, the hour and date, position of the patient, and presence of any significant circumstances such as taking of drugs or indulgence in exercise, etc.   Such a record has three important uses:

(1) It may be used by the technician to refresh his memory before testifying;

(2) In case the technician is unavailable, the record may be admissible in evidence as an entry made in the course of business, thus bringing the facts recorded within an established exception to the hearsay rule;

(3) In some states, the record may be offered in evidence as a business entry without producing the technician, even though he is available locally.

free of artefacts and portray a true and accurate picture of heart action without distortion introduced by extraneous factors.[11]

5. That the tracing is identified as pertaining to the particular subject.

6. That the tracings have been in his care or under his supervision from the time the pictures were made until they are offered in evidence.

Proper practice is to offer the authenticated electrocardiogram in evidence before permitting any opinion to be given interpreting it.

The electrocardiograms, so verified and vouched for as trustworthy, should be offered in evidence before any opinion is expressed upon them. The courts and workmen's compensation commissions should refuse to permit opinion evidence as to electrocardiograms which are not first offered in evidence.[12] This may be rested on a proper application of the best evidence rule.[13] The original tracing has primary value, whereas a mere

[11] See Esler, James W., and White, Paul D.: The distortion of the electrocardiogram by artefacts, Am. Heart Jr., 1929, iv, 296–304; Hartwell, A. S., Burrett, J. B., Graybiel, A., and White, P. D.: Effect of exercise and of four commonly used drugs on the normal human electrocardiogram, with particular reference to T-wave changes, Jr. Clin. Invest., 1942, xxi, 409–417.

In the New York conspiracy to procure payment of insurance disability benefits for simulated heart disease, policy holders were given moderate doses of digitalis. This was done prior to electrocardiographic examinations to be made by unwitting cardiologists. Some patients were even surreptitiously "dosed" while in hospital. In some cases the drug produced only a flattening of the ST intervals. In others, varying degrees of auriculoventricular block occurred. Premature contractions were frequently produced and in a few instances actual inversions of the T-wave occurred. The net effect was to produce an electrocardiographic tracing suggestive of heart damage.

One insurance company doctor, after reading an electrocardiographic tracing so produced, said: "If the patient is not taking digitalis, I would say that he is totally disabled."

Another insurance company doctor said regarding electrocardiographic tracings submitted in support of a different insurance claim: "Since digitalis administration has been denied, it must be assumed that this record is associated with myocardial damage of coronary origin."

Hedley, O. F.: The fraudulent use of digitalis to simulate heart disease, ANN. INT. MED., 1943, xviii, 154.

[12] X claimed workmen's compensation for cardiac disability allegedly due to accidental injury suffered from exposure to carbon monoxide in a mine, but an arbitrator made an award for the employer, finding that X's disability was due to chronic myocarditis. Dr. Y testified favorably to the employer, basing his opinion partially on electrocardiograms not produced in evidence, and the claimant, on this ground among others, sought to have the award set aside for misconduct of the arbitrator.

Held: As in case of roentgen-ray plates, the electrocardiographic picture should be produced before an expert opinion is given interpreting it, but since a Kansas statute provides that "the committee or arbitrator shall not be bound by technical grounds of procedure or evidence," nor is erroneous admission of evidence mentioned in the statute describing what constitutes "serious misconduct," this departure from proper practice is not a ground for setting aside the award.

Lefebre v. The Western Coal and Mining Co., 131 Kan. 1, 289 P. 456 (1930).

Electrocardiographic tracings are fully as complicated as roentgen-ray pictures, and the better view is that the latter must be offered in evidence before an expert opinion is given interpreting them.

Marion v. Coon Construction Co., 216 N.Y. 178, 110 N.E. 444 (1915). (Cited with approval in the Lefebre case, supra.)

Neill v. Fidelity M. L. Ins. Co., 119 W.Va. 694, 195 S.E. 860 (1938). A less desirable rule is that the physician, on direct examination, may give his opinion based on interpretation of roentgen-ray plates without simultaneously producing them, and that the opponent, on cross-examination, may require their production. Sullivan v. Minneapolis, St. P. & S. S. M. R. Co., 55 N.D. 353, 213 N.W. 841 (1927).

[13] The court in the Lefebre case, supra, seemed to consider the vice of non-production of the electrocardiographic tracing to be an infraction of the hearsay rule. This analysis hardly

description of it involves inferior secondary evidence and a conclusion of the interpreter, which independent experts and opposing counsel cannot reasonably test or cross-examine unless they have opportunity for inspection.

Electrocardiograms are taken directly on photographic paper, so that there are no negatives to be produced at the trial. This practice minimizes likelihood of fraudulent retouching or alteration of tracings. As an additional safeguard, the court should require at least 4 to 6 inches of each lead to be offered in evidence. This would afford several repetitions of each given configuration, thus minimizing still further any slight risk of artefacts or intentional distortion.

IV. PERSUASIVE AND PROBATIVE VALUE OF ELECTROCARDIOGRAMS

It is a fact well known to trial lawyers that visual or demonstrative evidence has a strong persuasive appeal for lay jurors. The reasons for this are various: the immediacy of demonstration through the eye, the avoidance of ambiguity and abstruse presentation, and the dramatic appeal, all contribute to this phenomenon.[14]

It is by no means certain that electrocardiograms will enjoy the same degree of jury appeal as some other species of demonstrative evidence. This is because the tracings are too complicated to be understood by the lay juror, and he can only accept the expert's interpretation. In some jurors this may arouse a sense of antagonism and a reluctance to give the electrocardiographic evidence the acceptance one might expect. These complications, however, are somewhat counterbalanced by the strong logical appeal, as the juror is bound to realize that a visible record made at the time "tends to pin things down" more completely than the distant recollection of an auditory experience.

From the standpoint of probative value it is obvious that electrocardiograms in their proper sphere are of great value because they substitute objective demonstration of a uniform character for variable subjective impressions. Furthermore, the tracing provides a permanent record and eliminates dangers which attend reliance on memory in the giving of testimony.

All of us know from personal experience that there are few, if any, absolute facts. One of the pitfalls in proving anything is to dispose of alternative inferences which might be drawn from a body of evidence and lead to utterly different conclusions. In this respect, proof in law and science are no different. Whenever a physician is to testify in court regarding electro-

fits in with the customary and historical concept of the hearsay rule as a prohibition against offering unsworn verbal testimony of a third person not present in court. That the vice is in withholding the best evidence, is shown by the decisions which permit a doctor to give an opinion on a roentgen-ray picture, without producing the latter if proof first be offered that the picture is lost.

Stiles v. McLean, Finch v. McLean, 103 N.J.Eq. 537, 138 Atl. 119 (1927);
Vale v. Campbell, 123 Or. 632, 263 Pac. 400 (1928).
[14] Smith, H. W.: Components of proof in legal proceedings, Yale Law Journal, 1942, li, 537.

cardiograms, he must acquaint himself and his lawyer with the diverse conditions which might produce the same or a substantially similar electrocardiographic tracing.   We cannot undertake here to give the electrocardiographic differential diagnosis on every conceivable medico-legal condition.   But in the trial of a particular case, the expert witness must be prepared to do so. If he is called by the plaintiff he will want to do this to satisfy himself and the court that his diagnosis and consequent prognosis are trustworthy and probably correct, rather than conjectural.   If he is advising the defense, he will expect the opposing witness to be held to the same scientific differential routine.

V.   The Value and Shortcomings of Electrocardiography

The electrocardiogram may yield objective information, not obtainable by any other means during life, on three aspects of heart disease:

(1) It may give direct proof of the presence, location and type of an abnormal rhythm, even if no demonstrable changes are evident at post mortem.

(2) It may give direct evidence of the presence of damage to the heart muscle.

(3) It may yield indirect confirmatory or illustrative evidence of the presence of certain types of pathologic lesions or the action of certain etiological agents.   This is true because some types of cardiac lesions (valvular, myocardial, pericardial or vascular) are frequently associated with certain electrocardiographic patterns, (e.g. left axis deviation in hypertension or aortic valvular disease) and some etiological agents are likely to result in specific types of cardiac disease (e.g. RS–T interval and T-wave changes in carbon monoxide poisoning or myocardial infarction).

The electrocardiogram, therefore, if positive, can be used to demonstrate that cardiac damage actually exists and in many instances it may yield confirmatory evidence concerning the type of damage.   If electrocardiograms are taken at appropriate times (preferably before and at frequent intervals after the injury), they may show objectively that cardiac damage occurred following that injury and perhaps that the type of damage sustained was the type likely to result from that specific form of injury.   Furthermore, it may be possible to infer that the type of cardiac damage illustrated by the electrocardiogram *may*, under certain conditions, result in cardiac symptoms or disability.

On the other hand, it is important to realize that it is impossible to state from the tracing alone that the alleged injury and nothing else resulted in the cardiac damage; or that the damage evidenced in the tracing necessarily resulted in cardiac symptoms or incapacity; or, where the electrocardiogram is normal, that cardiac damage or symptoms do not exist.   This is true because most electrocardiographic abnormalities can occur in several different

cardiac conditions; furthermore, an abnormal electrocardiogram does not *necessarily* mean poor cardiac function; and, also, cardiac damage does not *necessarily* show itself in the electrocardiogram. It must be pointed out, also, that medical opinion is divided as to the causal relationships between certain types of stimuli (trauma not involving the chest wall, physical over-exertion, fatigue, emotion, etc.) and cardiac damage or poor function.

VI.   USE OF THE ELECTROCARDIOGRAM AS EVIDENCE

In general, it is unwise to rest the diagnosis of a heart condition on the electrocardiogram alone, but, rather, the tracing should be utilized as part of the total available clinical evidence. The electrocardiogram can be used to obtain objective confirmation or illustration in regard to specific cardiac problems, but since most electrocardiographic abnormalities can occur in several different cardiac conditions, and since cardiac damage does not *neces-sarily* result in electrocardiographic abnormality, the significance of the electrocardiogram in the *specific* instance must be interpreted by properly trained and experienced individuals.

It is obvious that the main use of the electrocardiogram is to present objective confirmation of the presence of heart damage, and the time relationship between the alleged injury and the development of the cardiac damage. This usually requires interpretation or opinion of the specific electrocardiogram in relation to the specific cardiac problem.

It is evident that the electrocardiogram does not have the same probative value in all instances. In general we may divide the applications of the electrocardiogram into four classes ranging from high probative value in establishing heart condition to absence of probative value. The several classes of heart conditions which conceivably may confront the examiner are presented in table 1.

TABLE I

The Relative Importance of the Electrocardiogram in the Diagnosis of Heart Disease

Etiology	Pathology	Function
CONGENITAL III	DEVELOPMENTAL DEFECTS III	CONGESTIVE FAILURE IV
RHEUMATIC III	VALVULAR DAMAGE III	CARDIAC ASTHMA IV
SYPHILITIC III	ARTERIAL DAMAGE III	ANGINA PECTORIS IV
ARTERIOSCLEROTIC II	MUSCULAR DAMAGE	LIMITATION OF ACTIVITY IV
HYPERTENSIVE II	A. Degeneration or destruction	Causes of increase of cardiac
ASTHMATIC II	of the myocardium II	symptoms:
THYROTOXIC III	B. Relative myocardial weak-	Increase in pathologic lesions
PNEUMONIC III	ness (especially in a heart al-	IV
DIPHTHERITIC III	ready damaged) IV	Increase in work IV
		Abnormal rhythm I
TOXIC II	PERICARDIAL DAMAGE II	BACTERIAL ENDOCARDITIS IV
TRAUMATIC II	ABNORMAL RHYTHM I	

I. Diagnosis may be made by the electrocardiogram alone (see text).
II. Diagnosis usually, or frequently, is confirmed or corroborated by electrocardiographic evidence.
III. Diagnosis may be aided by the electrocardiogram under some circumstances.
IV. Diagnosis is not helped by the electrocardiogram.

1. *Instances where the diagnosis may be made by the electrocardiogram alone.* Here the evidence has its highest probative value, and on occasion may be entitled to conclusive effect, as against contradictory findings made by less reliable methods. These cases include the arrhythmias, or departures from normal rhythm in the heart beat.

In many of these instances the diagnosis cannot be made without positive electrocardiographic evidence, and in most cases the diagnosis can be made by the electrocardiogram alone, even without clinical examination of the patient. The electrocardiogram, however, usually tells little about the *cause* of the arrhythmia or the *amount of disability* resulting from it. Its value, therefore, consists in providing objective demonstration that abnormal heart action has occurred. The circumstantial value of this evidence clearly is enhanced if a person who attributes heart disorder to accidental injury can produce pre-traumatic electrocardiographic tracings showing that the rhythm of the heart was normal prior to the alleged incident.

2. *Instances where the clinical diagnosis may be confirmed by electrocardiographic evidence.* This group includes conditions where changes in the heart muscle occur due to hardening of the arteries, high blood pressure, chronic asthma, poisoning, forceful injury, or progression of underlying disease.[15] In this group the typical textbook picture of the clinical condition usually includes a typical electrocardiographic picture. A positive electrocardiogram, therefore, is important objective corroborative evidence of the existence of the clinical condition. The electrocardiographic picture, however, may not be specific for the condition under discussion, and therefore, the tracings must be interpreted as part of the entire picture. A normal electrocardiogram, as we have mentioned, does not necessarily disprove the existence of damage. Failure to obtain adequate electrocardiographic studies of such cases suggests incomplete study unless there are extenuating circumstances.

3. *Instances where the cardiac diagnosis may be aided indirectly by electrocardiographic evidence.* In this third category (table 1, III), the conditions themselves are not identifiable by a characteristic electrocardiographic pattern, but they may result in various types of cardiac abnormalities which do have characteristic electrocardiograms. For example, rheumatic stenosis of the mitral valve may be associated with the electrocardiographic picture of right axis deviation, whereas disease of the aortic valve may be associated with the picture of left axis deviation. Here again a normal electrocardiogram does not disprove the existence of pathologic lesions.

4. *Instances where the electrocardiogram throws no light on the specific cardiac problem.* This group is of considerable importance for it deals with the impairment of cardiac function or disability for which compensation is sought.

[15] Some leading major works on electrocardiography are: Pardee, Clinical aspects of the electrocardiogram, 1941, 4th Ed., Paul B. Hoeber, New York; Graybiel and White, Electrocardiography in practice, 1941, W. B. Saunders, Philadelphia; Katz, Electrocardiography, 1941, Lea & Febiger, Philadelphia; Katz, Exercises in electrocardiography, 1941, Lea & Febiger, Philadelphia.

On the basis of available knowledge, it is possible to make certain suggestions concerning the use of the electrocardiogram as evidence of the state of the heart.

Since the electrocardiogram should be used only in relation to the entire clinical picture as developed by well rounded examination of the heart, it is wise to look askance at any testimony in which the electrocardiogram is relied upon as sole proof of the presence of symptoms or disability.   This is true because a positive or abnormal electrocardiogram merely demonstrates the presence of cardiac abnormalities, and these may or may not result in symptoms or disability.   We continue to stress this point because of the evident danger that courts might be led erroneously to accept an abnormal tracing, alone, as adequate proof of a major cardiac disability due to an alleged injury.

The following actual problems of cardiac disability coming before courts and workmen's compensation commissions illustrate type situations where electrocardiographic evidence might be of value.

Group I: *Direct trauma to the heart, including heavy impact injuries to the overlying thorax.*

It is generally accepted that direct injury to the heart or chest wall may result in damage to the heart.[16]   Such damage will show itself in symptoms or signs of heart disease or dysfunction.   Electrocardiograms may yield objective proof of the existence or development of cardiac damage following injury.   The importance of taking such tracings at intervals appropriate to show the time relationships between the traumatic injury and the cardiac damage is evident.

Case 1: *Workmen's compensation insurance: alleged death from pericarditis.*[17]

[16] Master, A. M., Dack, S., and Jaffe, H. L.: The relation of effort and trauma to acute coronary occlusion, Indust. Med., 1940, ix, 359–364; Warburg, E.: Subacute and chronic pericardial and myocardial lesions due to non-penetrating traumatic injuries, 1938, Oxford Univ. Press, New York; Boas, Ernst P.: Angina pectoris and cardiac infarction from trauma or unusual effort, with a consideration of certain medicolegal aspects, Jr. Am. Med. Assoc., 1939, cxii, 1887–1892.

[17] The necessity for "education" of the lay jury and court in the medical problems involved is obvious in each instance.   The description below is not meant to be a complete discussion of pericarditis, but rather a presentation of those aspects necessary for better understanding of the rôle of the electrocardiogram in such cases.

Pericarditis (inflammation of the outer surface of the heart) may be caused by local infection (pneumonia, tuberculosis, rheumatic fever); reaction to the toxemia of kidney disease (uremia); inflammation or damage to the heart (myocardial infarction); or direct injury with or without perforation of the chest wall.   The diagnosis is based on:

(1) The finding of specific signs, especially a "friction rub" (a rough, grating, reduplicated sound synchronous with cardiac contraction and relaxation).   This is usually accompanied by symptoms of heart damage (pain, rapid heart rate, etc.) plus signs of inflammation (fever, elevated white blood cell count, elevated sedimentation rate, etc.).

(2) Objective evidence in the electrocardiogram.

The electrocardiographic picture may have one of three general forms:

(1) A characteristic upward sloping of the RS–T segment seen in any or all of the four leads.   This progresses rapidly (within days) to temporary inversion of the T-wave followed rapidly (within days) by return to normal.

(2) Progressive changes in the electrocardiogram, especially the RS–T segment or

X, a workman employed on a machine used to press copper bands around shells, fell on August 1, 1916, while carrying a load, and struck his chest on an iron lever. This caused pain and left a mark over his heart about five inches long. X received first aid treatment, and on being taken home that night went straight to bed complaining of pain in his left side and trouble in breathing. On the second day he came under care of physician Y, who testified that he found X suffering from pain in the left side of the chest in the region of the heart, with labored breathing, jerking whenever he took a long breath. He also found X's heart was laboring and heard an "abnormal sound" of the heart, and he testified that X's death in hospital on August 8, 1916, was due to "pericarditis" caused by the accident. X's past history showed no sickness except for a two week period a year previously, and he had worked steadily at general labor without any complaints about his heart or lungs. The employer insisted X did not die as a result of the accidental injury, but that his death was due to a disease, neither produced nor aggravated by such injury. Held: Death award made by Industrial Board affirmed.

Bucyrus Co. v. Townsend, 65 Ind. App. 687, 117 N.E. 656 (1917).

Comment: Was claimant suffering from cardiac disability?   The plaintiff X obviously had cardiac damage as shown by the doctor's findings on August 2 and thereafter.   The diagnosis in this instance rested on the clinical picture rather than on any tangible objective evidence.   Properly dated and identified electrocardiograms might have shown the characteristic RS–T segment or T-wave changes proving objectively that pericarditis or myocardial damage occurred immediately following the alleged injury.

2. Did the cardiac disability cause claimant's death?   This cardiac damage was the cause of death.   The electrocardiogram would give no specific information concerning the severity of the disease or prognosis of the individual patient, but it is generally agreed that the outlook is not good for persons with the clinical and electrocardiographic picture associated with pericarditis, and death frequently results.

3. Were cardiac disability and resultant death caused by an accident arising out of and in the course of employment?   The particular stimulus in this case was medically adequate to produce the injury.   While it is true that other conditions might have the same electrocardiographic pattern, all the evidence proved that no other cause existed, and the blow on the chest was the actual cause.   The electrocardiogram would give no evidence concerning the actual precipitating cause of the cardiac damage, but since the time of the accident was known and since medical attention was sought shortly thereafter, it would have been possible, by taking electrocardiograms at proper intervals, to show that in this particular instance the cardiac damage had the proper time relationship to all the relevant factual evidence, thus drawing all evidentiary data together faithfully into one mosaic.

T-wave, other than the specific upward sloping of the RS–T segment. *Obviously, to show the changes outlined in (1) and (2) the tracings must be taken at the appropriate times.*
(3) A normal electrocardiogram with no changes.

See Langendorf, R., and Goldberg, S.: The electrocardiogram in traumatic pericarditis, Am. Heart Jr., 1942, xxiv, 412–416.
Vander Veer, J. B., and Norris, R. F.: The electrocardiographic changes in acute pericarditis, Jr. Am. Med. Assoc., 1939, cxiii, 1483.

Case 2: Tort Case: *Recovery of damages for heart block attributed to heavy impact injury of thorax negligently inflicted by another.*[18]

A, owner of the ship *Italy Maru,* engaged in the lumber-carrying trade between west coast ports and Asiatic countries, hired B, a stevedore company, to load the vessel from railroad cars brought onto the docks. A also hired C, a middle-aged individual, to work between boat and car marking lots of lumber for their proper placement in the hold. Observe that C was not an employee of B; furthermore, since part of his work was aboard ship he was subject to maritime law rather than to the Workmen's Compensation Act of the State of Washington in respect to any injuries sustained.

B, in operating a loading boom, negligently brought a heavy timber against C as he was standing in a proper place on the railroad car. This serious injury occurred on February 11, 1922. The record does not show the interim medical history, but in the following November, C developed heart block, ventricular systole dropped to 32 per minute, and C became subject to fainting spells, so that he could not safely walk the streets without an attendant. Medical testimony was offered that C was totally and permanently incapacitated for gainful employment and that the heart block "either could be caused, or, if latent, could be rendered acute by the injury." A jury returned a verdict in favor of C against B, for $35,000, and on appeal judgment in this amount was affirmed.

McEachran v. Rothschild & Co., 135 Wash. 260, 237 Pac. 711 (1925).

Comment: Did a cardiac disability exist? It is evident that this workman C had heart block and this resulted in disability. The electrocardiogram would have furnished objective proof of the occurrence of heart block, even if postmortem examination revealed little. Indirectly the electrocardiogram would have helped prove the existence of cardiac disability due to heart block, for the clinical characteristics and fatal outcome of this condition are well known.

Was the cardiac disability caused by an accident arising out of and in the course of employment? This case illustrates the difficulties encountered when a long interval of time elapses between the alleged injurious stimulus and the alleged disabling result. Under such conditions every possible means of cardiac study should be used to prevent serious injustice to claimant or defendant. A single electrocardiogram would have been of little value in establishing a cause and effect relationship, for any abnormality observed might have antedated the injury, or might have resulted from natural aging

---

[18] Heart block is an abnormality of rhythm occurring physiologically when the usual rhythmical impulses which cause the heart to beat at the normal rate (about 72 beats per minute) are "blocked" or fail to stimulate the ventricles to contract. As a result, new impulses arise at a slower rate (about 30 to 40 per minute) from a new location.

This slow rate tends to reduce cardiac output of blood to a level insufficient to maintain normal physical activity. Furthermore, it is not uncommon for the heart to cease beating entirely or to beat erratically and inefficiently; as a result, loss of consciousness, convulsions and frequently death may ensue.

The causes of heart block are several and include age (arteriosclerosis), infections (syphilis, rheumatic fever), tumors, myocardial infarction, and damage due to trauma. In the latter case the heart block is likely to occur soon after the trauma but may be delayed in its appearance.

The electrocardiographic picture of heart block is typical and diagnostic. It consists of a complete dissociation between the usual impulses (P-waves) arising in the S-A node (which cause the heart to beat at the normal rate), and the new ventricular impulses (QRS and T-waves) arising in the A–V node or ventricle (which beats at the slow rate). The electrocardiogram tells little about the reason that the heart block has developed.

processes during the course of the illness and unrelated to the injury. Repeated interval electrocardiograms if obtained might, however, have shown the development of, or freedom from, interval cardiac damage.

Group II: *Indirect trauma, including peripheral injury.*

Such cases most commonly arise, as we have stated previously, in relation to Workmen's Compensation. The problem may also arise in tort cases where negligent or intentional acts cause peripheral injury culminating in cardiac disability.

Expert medical opinion will frequently disagree on the relationship between such overexertion, fatigue or indirect trauma and cardiac damage, especially if there is an appreciable lapse of time between the alleged incident and the cardiac result. Obviously, all means available should be pressed into service to obtain all possible objective data relative to the cardiac condition. These considerations make advisable initial and interval electrocardiograms, and possibly also hospitalization, for *all* workers who collapse in the course of their employment or shortly thereafter.

Case 3: *Workmen's compensation: angina pectoris and coronary thrombosis imputed to excessive strain from long hours of clerical work, without traumatic injury.*[19]

X, a 48 year old claim adjuster, subject to arteriosclerosis, worked progressively harder, day and night, for nine months. This was made necessary by the great increase in claims to be adjusted from about 100 per month (a full load for an adjuster) to about 250 per month. X became very fatigued by this excessive exertion. He also developed nervous strain as a result of constant complaints from his employer about slowness in settling claims. He became subject to frequent violent headaches, heartburn and fatigue, and on April 28, 1934, allegedly suffered an attack of angina pectoris, followed on May 5, 1934, by a coronary thrombosis which totally incapacitated him. The employer vigorously contended that there was no "accidental injury" arising out of the employment. A doctor testified that "My opinion is that excessive work and strain induced a premature change in his coronary system." He further testified that overwork, worry and emotional strain induced a spasm in a susceptible coronary artery and resulted in the disturbance of the vasomotor system bringing about angina pectoris. A Compensation Commission made an award. Held, on appeal: Affirmed.

[19] *Clinical Picture and Definition of Terms.* According to present concepts, angina pectoris (heart pang) occurs in persons whose arterial blood flow to the heart muscle (coronary circulation) is unable to respond adequately when additional blood is needed. When the *supply* of blood to the heart is inadequate for the *demands* of the heart muscle, a state of relative anoxemia (oxygen deficiency) results, and the patient experiences heart pain. The most common cause of such an inadequate coronary circulation is arteriosclerotic narrowing of the coronary arteries. The most common causes for precipitating attacks of angina pectoris are exercise and emotion. With cessation of the precipitating exercise or emotion, the discrepancy between demand and supply of blood ceases, the physico-chemical changes secondary to anoxemia reverse themselves, and the pain disappears. Under conditions of physical or emotional fatigue, attacks of angina pectoris may occur more frequently.

If anoxemia persists for a sufficiently long period of time (due to complete occlusion of a coronary artery or to prolonged angina pectoris), the physico-chemical changes become irreversible and permanent damage to the heart muscle occurs. This destruction of heart muscle is called *myocardial infarction.* Since it is due usually to coronary occlusion or coronary thrombosis, these terms are frequently used interchangeably.

The electrocardiographic picture of myocardial infarction is quite typical. It consists in most cases of changes of the RS–T segments and T-waves progressive over days or weeks; in other instances, transient arrhythmias may indicate involvement of the ventricular muscle. Since these changes are transient and progressive, tracings should be taken soon after the onset of the illness and frequently thereafter.

The circumstances leading up to injury were equivalent to overexertion or excessive muscular strain in a day laborer, and the disability was therefore compensable as an "accidental injury."

Hoage v. Royal Indemnity Co. (Ct. of App. D.C.), 90 F.(2d) 387 (1937).

Comment: Was the claimant suffering from myocardial infarction and angina pectoris? Because of the typical clinical and electrocardiographic picture of myocardial infarction there should be no difficulty in showing that this occurred. The problem is quite different in angina pectoris for here there may be no clinical or electrocardiographic evidence of heart disease, even though the condition is advanced and there is marked incapacity.

Since angina pectoris is usually due to coronary arteriosclerosis, about one half of the patients may show one or more of the many electrocardiographic abnormalities seen in this condition, but about one fourth of the patients may show no evidence indicating heart damage.[20] Recently, attempts have been made to utilize the electrocardiogram during or after exercise or during generalized anoxemia (induced by breathing an atmosphere poor in oxygen content), as a test for the presence of coronary insufficiency. There is no uniformity of opinion, however, concerning the practical value of such studies. Levy et al.[21] and Masters et al.[22] believe that a positive result is of value, yet Riseman et al.[23] have shown that these changes are so rapidly progressive that tracings cannot be taken under conditions permitting comparison, and, furthermore, that the difference between the response of normal subjects and those with heart disease may be so slight that the test may be of little practical value in those borderline or controversial cases where further evidence is most needed.

The problem of incapacity due to angina pectoris frequently raises problems under clauses of insurance policies which promise benefits and waiver of premiums during disabilities. In those cases of alleged incapacity from angina pectoris where the insurance company has demanded electrocardiograms and found them negative, this obviously is not proof positive of nonexistence of that disease, and the inquiry will need be broadened to gather all lay and clinical evidence available concerning the nature of the complaint. If electrocardiograms are positive, the insurance company may be aided in coming to a more speedy recognition of the merits of the claim. It is interesting to note that electrocardiograms are becoming increasingly important in the conduct of the insurance business, both in respect to appraising

---

[20] Riseman, J. E. F., and Brown, M. G.: An analysis of the diagnostic criteria of angina pectoris, Am. Heart Jr., 1937, xiv, 331.

[21] Levy, R. L., Bruenn, H. G., and Russell, N. G.: The use of electrocardiographic changes caused by induced anoxemia as a test for coronary insufficiency, Am. Jr. Med. Sci., 1939, ccxli, 241; Patterson, J., Clark, T., and Levy, R.: A comparison of electrocardiographic changes observed during the anoxemic test on normal persons and on patients with coronary sclerosis, Am. Heart Jr., 1942, xxiii, 837.

[22] Masters, A. M., Friedman, R., and Dack, S.: The electrocardiogram after standard exercise as a functional test of the heart, Am. Heart Jr., 1942, xxiv, 777.

[23] Riseman, J. E. F., Waller, J. V., and Brown, M. G.: The electrocardiogram during attacks of angina pectoris, its characteristics and diagnostic significance, Am. Heart Jr., 1940, xix, 683.

the risk in regard to elderly or doubtful subjects applying for insurance, and in determining the merits of claims for benefits.[24]

To what extent, if any, did claimant's heart condition disable him? The incapacity due to heart disease is clear in this case from the clinical history. The electrocardiogram would throw little light directly on this or any other specific instance, although it is generally agreed that coronary thrombosis is frequently followed by incapacity for doing work which was possible previously.

Was cardiac disability caused by an accident arising out of and in course of employment? It is generally agreed that attacks of angina pectoris in susceptible individuals are more common under conditions of fatigue, overexertion or emotional strain. There is considerable difference of opinion as to the causal relationship between such stimuli and the precipitation of coronary thrombosis. Routine electrocardiograms throw no light on this problem. In each instance, therefore, the final expert opinion must rest upon skilled and informed judgment applied to the whole mosaic of evidentiary data.

Group III: Exposure of the heart to noxious agents carried in the blood stream, such as carbon monoxide or other poisons.

Case 4: *Workmen's compensation insurance: death from endocarditis allegedly accelerated by inhaling carbon monoxide gas.*[25]

X, an individual long subject to endocarditis, was a repair man in an automobile shop. Early in 1920 he went to work in the test shed where a number of cars were being tested constantly with engines running. During his work in this test shed, from time to time he was affected by the gas and went outside for relief. In particular, upon June 4, June 14, and June 22, 1922, he had experienced this trouble. On June 14 he left his place of work, went outside and was dizzy and faint. He was taken home, returned to work upon the 19th, worked about two days and on the 22nd again suffered from the effects of the gas or his heart trouble, and thereafter did not return to work. X died on October 4, 1924, of endocarditis. Claim was made for death benefits. The case had a protracted course before the Industrial Board and the New York courts, with an award finally being entered in favor of X's legal representatives on the theory that accidental carbon monoxide poisoning operated to cause death by substantially accelerating preexisting endocarditis. The trial court found that: "The progressive and active condition of endocarditis, from which the deceased died on the 4th day of October, 1924, was naturally and unavoidably the result of the inhalation of carbon monoxide gas at his employer's test shed on June 14, 1922. He had a preexisting condition of the heart and the disturbance caused by the toxemia, or poisoning, which in this case was produced by the inhalation of the said carbon monoxide gas, superimposed upon the deceased's preexisting heart condition, caused degeneration of the

[24] Taylor, H. F.: The value of electrocardiography in medical underwriting, Proc. Assoc. Life Insur. Med. Dir. America, 1932, xviii, 165–201; Wilson, F. N.: Recent progress in electrocardiography and the interpretation of borderline electrocardiograms, Proc. Assoc. Life Insur. Med. Dir. America, 1938, xxiv, 96–156.

[25] *Carbon Monoxide Poisoning and Electrocardiographic Evidence.* Carbon monoxide poisoning results in impaired capacity of the corpuscles to transport oxygen, and the heart suffers from anoxemia. If the dosage of carbon monoxide be sufficient, heart damage will result, and this may be more extensive in the presence of a preexisting endocarditis, so as to warrant a professional opinion that the latter was substantially aggravated by the accidental poisoning. A number of cases of cardiac damage through carbon monoxide poisoning have been arising in the workmen's compensation field, and papers have been written devoted to specialized aspects of the electrocardiographic configurations one may expect to find.

deceased's heart muscles and in turn deceased's death from endocarditis. . . ." A very strong contention was made that no definite date of an "accident" had been proved, and that any effects of the carbon monoxide were at most transient and did' not accelerate the endocarditis. By a 3–2 decision, the New York Appellate Division affirmed the award.

Reichard v. Franklin Manufacturing Co., 223 App.Div. 797, 228 N.Y.S. 17 (1928), affirmed without opinion in 249 N.Y. 525, 164 N.E. 570.

Comment: The electrocardiogram would give no direct evidence of the presence of endocarditis. The presence of carbon monoxide poisoning of the heart muscle would be shown objectively by the presence of progressive or permanent changes (especially in the RS–T segment and T-waves) similar to that seen in myocardial infarction.[26]

The electrocardiogram, therefore, if taken at the proper time, should provide objective evidence of carbon monoxide poisoning. The Reichard case is one of those where lack of a specific incident and long lapse of time between stimulus and final injury cause natural doubts to arise about causal connections. Electrocardiographic tracings made at once after the initial collapse and at intervals thereafter might well throw valuable light on the cause-effect relationships.

Group IV: Injuries ascribed to psychosomatic stimuli, consisting of nervous shock without substantial impact, or other psychic factors.

The stimulus would need to represent something more than the usual tensions of that type of employment to satisfy the legal definition of an "accident."

Case 5: *Workmen's compensation: Death attributed to acute dilation of heart from shock, excitement and overstrain caused by accidental breaking of steam pipe on crane operated by workman.*

Employee, X, a workman with preëxisting heart disease, was operator of a revolving steam crane mounted on a flat car and used for handling logs. A steam pipe which projected over the end broke. "A dense cloud of escaping steam immediately enveloped the decedent, who was in the cab. The boiler was carrying a capacity load of steam, and, fearful of an explosion, he attempted to pull the fire from under it. He had a weak heart, and it is claimed that because of the shock and excitement, due to the sudden escape of the steam and the fear of the explosion, he became physically unable to put out the fire. He called a fellow workman to assist him, then got out of the cab, and sat down on a log apparently much exhausted. In a few minutes he got into his automobile and drove home. After dinner he rested awhile before driving back to the place where he was employed. He remained there for a few minutes, then returned to his home. Arriving there he rested in bed for two hours. After he arose, he attempted to do some work in mending a chair, but complained of feeling 'done for.' A few minutes later he dropped dead. This was about 4 o'clock in the afternoon. The accident happened at 11:30 a.m. A claim for compensation was made. The defendant denied liability on the ground that there was no accident and no injury and no causal connection whatever between decedent's death and his employment. On the hearing, the commission decided against this contention and filed an award for compensation in the sum of $14 per week for 300 weeks."

[26] Stearns, W. H., Drinker, C. K., and Shaughnessy, T. J.: Changes found in 22 cases of carbon monoxide poisoning, Am. Heart Jr., 1938, xv, 434–447.

No postmortem examination was made. X's family physician gave it as his opinion that "The probability is that the final cause was acute dilation of the heart brought on by overstress and overstrain and excitement."

Held, on appeal: Award affirmed. The court stressed the shortness of the time interval separating stimulus and death, and the fact that X was constantly sick during that period. "The fact that he [X] had a previous disease of the heart, which may also have contributed to his death, is immaterial. The shock and excitement were concurring causes. It is not necessary that they should have been the sole, proximate cause."

Monk v. Charcoal Iron Co., 246 Mich. 193, 224 N.W. 354 (1929).

Case 6: *Tort case: Wrongful death action on behalf of guest against driver for negligently causing automobile accident which allegedly caused guest nervous shock and resultant heart failure.*

B, a 28 year old girl, was riding in the car of C when the latter negligently ran off the traveled highway and tipped over. B suffered various injuries, including nervous shock. Seventeen days later she died of "heart failure." Her administrator sued C for wrongfully causing her death. All admitted that B had suffered from preexisting heart disease, and defendant C maintained that her death was due solely to it and not to the accident. Plaintiff's doctors testified that the nervous shock of the accident aggravated her heart condition and led to her death. No electrocardiograms were offered in evidence. Verdict and judgment in favor of B's administrator for $2,800 was upheld on appeal.

Albrecht v. Potthoff, 192 Minn. 557, 257 N.W. 377 (1934).

Comment: Obviously it is difficult to establish a cause and effect relationship in such cases. The physiological mechanisms involved are many and will differ depending on the factors and the preëxisting cardiac damage involved in each case. In some instances, however, electrocardiograms may show definite progression of disease or new pathologic lesions following the emotional strain.

At present, the best authenticated type of cardiac disaster due to psychosomatic stimuli is an attack of angina pectoris precipitated by a sudden excess of emotion in one already subject to that disease. Provident and habitual taking of electrocardiographic tracings in cases of collapse following emotional stimuli may help elucidate any cause-effect relationships in respect to other cardiac conditions.

Group V: Miscellaneous medico-legal uses of the electrocardiogram.

A. THE ELECTROCARDIOGRAM FOR IDENTIFICATION PURPOSES

Sir Thomas Lewis first pointed out identifying properties of electrocardiograms. He said: "The similarity between the electrocardiograms taken from the same subject on different days is so close, and the variations from subject to subject are so numerous (for it may be said that no two series of curves are ever identical), that a series of three leads from any subject would be sufficient to identify the subject in question amongst a considerable number of his fellows." [27]

[27] Lewis, T., and Gilder, M. D. D.: The human electrocardiogram: A preliminary investigation of young male adults, to form a basis for pathological study, Philos. Trans. Roy. Soc. London, Series B, 1912, ccii, 351–376. See also Castellanos, I.: Personal identification by electrocardiography, Jr. Crim. Law and Criminol., 1932, xxiii, 356–360.

Any practical use of the electrocardiogram for identification purposes has been limited by obvious deterrents. It calls for special apparatus, for a technical procedure, and for a skilled interpreter, and further difficulties are introduced by the fact that minor variations do occur in individual patterns from various causes, as we now know. The method would be expensive in money and time as compared with other available means of identification. Furthermore, it would not be useful unless earlier comparison electrocardiograms were on file, an ideal which has not even been attained in the easily executed practice of identification by finger printing. Again, the electrocardiogram could not be used after death of the subject, and the intervention of any cardiac disease in the course of years would radically alter the electrocardiographic configurations.

The identifying properties of the electrocardiogram may assume importance, however, in individual litigation. In the notorious New York conspiracy scheme for simulating heart disease in order to collect insurance disability benefits, X, an insured person, proffered to the insurance company abnormal electrocardiographic tracings allegedly made when he was in hospital on a given date. Careful investigation showed that the tracings were not made at that time, but were made privately a month later, probably after the subject had been digitalized to distort his electrocardiographic tracings. This fact was established by the seizure of other like tracings found in the office of the incriminated doctor. The configurations of the tracings were so near to identical that no doubt existed regarding the certainty of proof. If it should be doubted that the electrocardiograms offered in court were taken from the plaintiff or claimant, there is no reason in most states why the court could not appoint an impartial physician to make new tracings. Usually these would show enough points of similarity or dissimilarity to settle the question of suspected substitution of electrocardiograms.

B. PREËXISTING ELECTROCARDIOGRAMS AS EVIDENCE OF PREËXISTING CARDIAC DISEASE.

If a person seeking insurance fraudulently conceals preëxisting disease which is material to the risk, courts will permit the insurance company to tender back premiums and obtain cancellation of the policy on the ground of material breach of warranty or fraud. If the assured, in applying for a policy, allegedly suppressed any information regarding prior heart disease, discovery of the fact that previously he had been the subject of electrocardiographic studies would be a most important circumstance going to show guilty knowledge. This is because, at the present time at any rate, it is not a universal custom to make routine electrocardiograms of patients. Some clinicians include this as a part of a routine physical examination of middle aged or elderly individuals, but in the hands of the general practitioner, it is usually a diagnostic refinement utilized only when good grounds exist for suspecting disorder or disease of the heart. It would be open to the assured to dispel inferences of guilty knowledge by producing the electrocardiograms and

showing them to be normal, or to otherwise prove that facts of his heart disease were not communicated or known to him.

CONCLUSION

We have endeavored in this paper to show what are the main sources of cardiac litigation, to point out basic legal principles important to the problem of proof and to analyze type cases where electrocardiography might be used in court. In doing this we have sought to stress important positive uses of the electrocardiogram while at the same time pointing out great variations in the probative value of this new species of evidence depending on the individual cardiac condition involved. We have stressed, as others have done, the interdependence of electrocardiographic interpretation on sound clinical examination and judgment. It is necessary to shatter any illusions that the electrocardiogram has universal diagnostic authority. It is only by recognizing the critical limitations of a new species of evidence that courts may protect against abuse and injustice likely to arise from extravagant claims regarding its virtue as proof.

PROCEEDINGS OF AMERICAN RHEUMATISM ASSOCIATION, ATLANTIC CITY, JUNE 8, 1942 *

ABSTRACTS AND DISCUSSIONS OF PAPERS

EPIDEMIC RHEUMATIC FEVER †

By PAUL L. BOISVERT, M.D., *New Haven, Connecticut,* M. HENRY DAWSON, M.D., *New York;* FRANCIS F. SCHWENTKER, M.D., *New York,* and JAMES D. TRASK,‡ M.D., *New Haven, Connecticut*

EPIDEMIC rheumatic fever is not a new disease but it does have especial importance in times, such as these, when large numbers of men are concentrated in military cantonments. The term, epidemic rheumatic fever, apparently implies more than is intended. It is used to indicate the presence of a significant number of cases under, as you might say, one roof. If rheumatic fever were a reportable disease in civilian life, it might be found that there would be considerable variations in its incidence from year to year.

Rheumatic fever is an important military disease and its presence offers a new approach to the study of the factors concerned with its production. Data from such studies carried out in Army Camps indicate that there is a strong association between hemolytic streptococcal infections and rheumatic fever. It seems impossible to distinguish between studies on rheumatic fever and those on the control of streptococcal disease in general.

We are much impressed with the care which the rheumatic fever patients receive in the Army Hospitals. Care, according to present-day standards, is excellent.

AN EPIDEMIC OF HEMOLYTIC STREPTOCOCCUS INFECTION AND RHEUMATIC FEVER AMONG NAVAL TRAINEES

By CAPT. R. M. LHAMON, (M.C.) U.S.N., LT. R. H. HUNTINGTON, (M.C.) U.S.N.R., STAFFORD M. WHEELER, M.D., and T. DUCKETT JONES, M.D., *Boston, Massachusetts*

Publication of this paper was withheld.

Discussion on paper of Dr. Boisvert, et al., "Epidemic Rheumatic Fever," and Capt. Lhamon, et al., "An Epidemic of Hemolytic Streptococcus Infection and Rheumatic Fever among Naval Trainees."

DR. J. R. PAUL, New Haven, Connecticut: It seems to me that the importance of these studies can hardly be overestimated, particularly at this time. They represent the first military epidemics of rheumatic fever that have been observed and studied in this country. That similar situations have existed for many years is evident from the literature from European sources. In past years the British, Italian, French, and German medical literature record so-called epidemics of rheumatic fever among troops, although few analyses were made of these situations. The point was that they exist. That they cannot only occur here, but that they can be extensive, seems evident from this paper, in which an epidemic of 145 cases is described among three others. That they can be studied is obvious and one cannot help feeling that such studies will eventually tell us more about the nature of rheumatic fever, for this problem is now subject to attack from the epidemiological point of view. The first problem is whether the epidemiology of hemolytic streptococcal infections and rheumatic fever are one and the same. Maybe we have been wasting our time in trying to make two diseases out of one.

The late Dr. Trask always maintained that the secret of rheumatic fever would be found in the study of scarlet fever and its complications, and that prediction is coming to the fore in these papers. Scarlet fever is the most spectacular and important of the streptococcal group because it is more definite; it has a rash and is more easily diagnosed. It is the cornerstone of streptococcal infections, as far as the epidemiologist is concerned. Another point is that although rheumatic fever apparently appears sporadically after German measles and other non-streptococcal infections, no epidemics of rheumatic fever have occurred unless they have been in close association with hemolytic streptococcal epidemics.

DR. M. J. SHAPIRO, Minneapolis, Minnesota: These two studies emphasize several important points: namely, that crowding intensifies the severity of an epidemic; that introducing uninfected individuals into an infected environment prolongs such an epidemic. This latter point is important in civil as well as in military life. Frequently when an epidemic of contagious disease occurs in a community, the question of whether or not to close the schools becomes a real issue. The present investigation suggests that the schools should be closed when an epidemic occurs.

These reports again emphasize the probability that the streptococcus is the cause of rheumatic fever. Each speaker seems to be about to state definitely that this has been proved. No such proof, however, is yet available. I agree that the streptococcus has something to do with rheumatic fever, but it cannot yet be proved that the streptococcus is the cause of rheumatic fever.

A point of interest was the statement that of 38 cases of rheumatic fever 31 per cent gave a history of previous rheumatic fever. A number of the patients who developed rheumatic heart disease during this epidemic gave evidence of having had cardiac involvement previously. It is apparent that some of the trainees with rheumatic heart disease were incorrectly diagnosed on their entrance examinations. The incidence of cardiac involvement (64 to 67 per cent) in this group of young men between the ages of 17 to 20 seems unusually high, but when it is noted that a considerable number of them had had previous rheumatic infection, the rate does not appear unreasonable.

DR. A. S. GORDON, Brooklyn, N. Y.: I would like to ask Dr. Jones whether, in view of the present investigation, he would be brave enough to put himself on record as to the etiologic relationship between the streptococcus and rheumatic infections generally, and rheumatic fever in particular.

DR. MAY G. WILSON, New York City: There is another factor to be considered in the epidemiology of rheumatic fever. As Dr. Boisvert has said, since rheumatic fever is not a reportable disease we have no knowledge of fluctuations in incidence in the civilian population. It happens that we have had 105 rheumatic families under observation over a period of 20 years. We were interested in learning whether there was a rise or fall in the prevalence of rheumatic fever. The analysis showed that there was no excess of cases over the number expected on an age and genetic basis for any calendar year over the 20 year period. There was no evidence of a cyclic change or epidemic phase. I think that if Dr. Boisvert would subject his data to further mathematical analysis he might be able to account for the low incidence he observed in the third camp. One can speculate that the prevalence of rheumatic fever is 1, 2 or 3 per cent, and that of these perhaps only 25 per cent did not have heart disease or had it to such a degree that it was not recognized when they were inducted. In this way, a rough estimate might be obtained and he might find that he had just as many as would be expected in the last camp. In our analyses recurrences were not studied, only onsets of the disease.

DR. PHILIP S. HENCH, Rochester, Minnesota: As a rule, those physicians who write about rheumatic fever are not particularly interested in the chronic arthritides, and those who study the latter diseases do not concern themselves especially with rheumatic fever. It would appear as if we had specialists in acute rheumatism distinct from specialists in chronic rheumatism. This separation of interests is unfortunate, for more comparative studies of both acute and chronic cases would doubtless uncover information of much value.

About three weeks ago I had the opportunity of visiting a mid-western naval station where I saw in one day about 110 young sailors with acute rheumatic fever. This single group of 110 youngsters, age 19 to 25 years, each with acute or recurrent rheumatic fever, represented an economic loss to the country of perhaps one or two million dollars in disability pensions and lost salaries and services for the present and future. Unfortunately, the medical authorities in charge were greatly handicapped and limited in what they could do to prevent a further spread of the condition, and laboratory facilities were not adequate enough to permit the institution of any extensive research studies on those already sick with rheumatic fever and on contacts or possible susceptibles. When such outbreaks occur in an army or naval station, what can the medical officer do to restrict its spread, or what can be done in a prophylactic way? I should like to ask Drs. Jones, Paul, and Boisvert for their comments on what those of us who are about to enter military service should do and what chance there is for such military stations to obtain the help of one of the research teams sponsored by the National Research Council.

DR. JACOB S. KOMINZ, Rochester, N. Y.: I have been in practice long enough to observe one factor of this disease. When I started to practice acute rheumatic fever was very common. I found it in stove heated homes. Since improvement in living conditions among families I find acute rheumatic fever is on the downgrade. I find it still in the home where they use an open stove. I wonder whether that plays a part in the barracks which I understand are heated by open stoves. I would like to ask whether there is any connection between rheumatic fever and that type of heating?

DR. ANN G. KUTTNER, Irvington, N. Y.: We have been studying rheumatic fever in a convalescent home for rheumatic children during the past five years. No rheumatic relapses were observed following the "common" cold, epidemic influenza or chickenpox.

During the first year, 1937–1938, 12 of the 108 children in the institution developed pharyngitis due to a Group A hemolytic streptococcus of a single type. Following a latent period six of these 12 children developed rheumatic manifestations.

The following winter, 1938–1939, a larger outbreak of streptococcal pharyngitis occurred during which 32 children developed upper respiratory infections associated with a single type of streptococcus, type 4. Although these cases of pharyngitis were more severe than those observed during the previous winter, not a single child developed rheumatic sequelae. During the winter of 1939–1940 a third outbreak of streptococcal pharyngitis was observed, this time due to Group A streptococcus, type 27. Of the 39 children who developed this infection, eight developed rheumatic recurrences.

Although no rheumatic recurrences were observed in children who escaped streptococcal pharyngitis, not every child who had this type of infection developed rheumatic manifestations and the total number of rheumatic recurrences occurring in the three year period was small. It seemed possible, therefore, that the relationship of the streptococcal pharyngitis to the reactivation of the rheumatic process might have been accidental. To rule out this possibility it was essential to study the effect of preventing streptococcal upper respiratory infections by some means which had no immediate influence on the rheumatic process itself. For this purpose sulfanilamide was chosen, since most observers agree that this drug not only fails to benefit patients with active rheumatic fever, but actually tends to increase the severity of the rheumatic symptoms.

During two successive winters, 1940–1941 and 1941–1942, the 108 children were divided into two groups, matched as closely as possible in regard to age, number of previous rheumatic attacks, and cardiac findings. Beginning in October and continuing until June, half the children were given prophylactic doses of sulfanilamide. The other 54 children served as controls.

During the winter of 1940–1941 thirty cases of streptococcal pharyngitis occurred among the 54 children in the control group. Fourteen of these 30 patients developed rheumatic relapses. During the winter of 1941–1942, 18 children in the control group of 50 developed streptococcal pharyngitis and nine of these showed rheumatic sequelae.

Among the children receiving sulfanilamide during the two winters, only two children developed streptococcal pharyngitis and only one of them showed mild rheumatic manifestations.

The studies, aside from showing the prophylactic value of sulfanilamide in preventing rheumatic relapses, indicate that the relationship between streptococcal pharyngitis and the reactivation of the rheumatic process is specific and establish the importance of Group A hemolytic streptococci as a factor in the etiology of rheumatic fever.

LIEUT. COMMANDER LeMOYNE C. KELLY (M.C.) V–(S), U. S. N. R., Portsmouth, Virginia: A great many of our patients at the Norfolk Naval Hospital have been in the sick bay of a ship for three to four weeks and by the time they reach us are apparently well. There is no objective evidence of disease such as swelling or any laboratory confirmation. I wonder if Dr. Paul and Dr. Jones would give us the benefit of their advice as to how long we should keep such patients on strict bed rest, because it is often quite a problem. The ships' officers are naturally anxious to have their men returned to duty and the Ward medical officer is the one who has to decide when that can be done with safety.

DR. M. HENRY DAWSON, New York City: Epidemics of rheumatic fever occurring among soldiers or sailors in training camps obviously differ in many respects from epidemics of the disease observed in institutions designed for the care of rheumatic subjects. In the latter case presumably every patient is at least potentially susceptible, and the incidence of rheumatic recurrences following hemolytic streptococcal infection will be relatively high. In the former case relatively few will be susceptible and the attack rate will be relatively low, no matter how widespread the

epidemic of hemolytic streptococcal infection may be. It is precisely because of this fact, however, that a study of the type of epidemic seen in the armed forces should yield particularly interesting information.

Epidemics of rheumatic fever are apparently prone to occur among young recruits, particularly among those undergoing intensive training in concentrated areas. A rapid change in personnel with the constant addition of fresh batches of recruits at periodic intervals seems to favor epidemic conditions. The two speakers unfortunately did not have time to refer to two very interesting papers on epidemic rheumatic fever recently published in England. In the first of these Green showed that among the trainees studied the only infection which led to the appearance of rheumatic fever was hemolytic streptococcal infection. He furthermore stressed the importance of a rising population in the maintenance of the epidemic. The second study by Thompson and Glazebrook (1941) was a detailed report on an epidemic of hemolytic streptococcal infection which persisted for 15 months among 2,095 trainees. The average population was some 1,200 and in all there occurred 1,903 cases of tonsillitis. Of these 115 developed clinical rheumatic fever. During the same period 1,243 examples of the common cold were observed but in no instance was this disease followed by rheumatic fever.

COMPARISON OF THE PATHOLOGY OF RHEUMATIC FEVER AND RHEUMATOID ARTHRITIS

By GRANVILLE A. BENNETT, *Boston, Massachusetts*

THE present observations are based on the findings in 150 surgically treated and 48 and 101 autopsied cases of rheumatoid arthritis and rheumatic fever subjects, respectively. This material has been supplemented by numerous biopsy specimens of various lesions, particularly subcutaneous nodules.*

Rheumatic Fever. Some degree of rheumatic carditis was found in all the 101 autopsied cases, and the Aschoff nodule was found in 67 instances. Of the remaining cases, 29 showed myocardial cicatrices, probably healed Aschoff nodules. Eleven patients (nine females and two males) between six and 29 years of age died with bacterial endocarditis and the hearts of four of them showed Aschoff bodies.

Macroscopic changes indicating old or recent pericarditis or both were present in 70. In 33 instances there was either complete or nearly complete obliteration of the pericardial space. Extrapericardial adhesions were found in 40 of the present series.

Although exudative and proliferative changes in the articular tissues of rheumatic fever subjects have been described by others, their incidence in the present series was small. Knee joints known to have been afflicted were examined in 11 of these patients and in four others. Pathological changes were observed in only three instances. In two there was a mild chronic synovitis of non-specific character. The third patient had presented a

* The majority of these cases were studied in the Arthritis Clinic of the Massachusetts General Hospital or at the Rheumatic Clinic of the House of the Good Samaritan by Drs. Walter Bauer and T. Duckett Jones during the past 12 years.

clinical picture that was difficult to distinguish from mild rheumatoid arthritis, and for this reason is described in some detail. She was a woman 45 years of age, who had been told that she had rheumatic fever and rheumatic heart disease five years before her last hospital admission. She had complained periodically of pain and stiffness in most of her joints during the previous five years. On several occasions tenderness, swelling and limitation of motion were elicited in the digital joints. Postmortem examination revealed the typical valvular, myocardial, and pericardial lesions of rheumatic heart disease. Examination of the spine, knees, metatarsophalangeal and interphalangeal joints of the most severely affected toes and the metacarpophalangeal and interphalangeal joints of one affected finger revealed a mild diffuse lymphocytic, plasma cell and mononuclear leukocytic infiltration in the synovial and subsynovial tissues. All other articular structures were negative.

Rheumatoid Arthritis. Postmortem examinations of 48 rheumatoid subjects have revealed that the most constant and significant pathological changes are confined to the skeletal system. Inflammatory lesions characterized by hyperemia and a marked diffuse lymphocytic and plasma cell infiltration of the subsynovial tissues, frequently accompanied by the formation of lymphoid follicles, were the earliest alterations noted. The synovial villi were redundant and thickened and occasionally showed areas of "fibrinoid" degeneration. Little or no fibrinous exudate was found on the synovial lining tissue regardless of the duration of the arthritis. As the disease progressed the chronic inflammatory and proliferative changes in the synovial tissues increased, extending from the perichondrial margins on to the articular surfaces. Later the joint cartilages were reduced in thickness, disrupted and finally partially or completely destroyed. Inflammatory changes of a similar type were frequently observed in the tendon sheaths. Bone atrophy was a constant finding. Localized bone destruction in the subchondral cancellous portions or shafts was frequently noted. Such lesions were usually the result of direct extension of inflamed connective tissue through the eroded articular surfaces or ingrowth along blood vessels through the bony cortex near the articular margins. Varying stages of fibrous and bony ankylosis were observed. Involvement of the terminal phalangeal joints was a frequent finding.

The cause of death in these 48 cases was as follows:

Cause of Death	Cases
1. Heart disease	
a. Coronary artery occlusion	5
b. Bacterial endocarditis	2
c. Myocarditis and aortitis (unknown etiology)	3
d. Cardiovascular syphilis	1
2. Pneumonia	8
3. Central nervous system lesions (hemorrhage and softening)	6
4. Malignancy	5
5. Tuberculosis, nephritis, sepsis and gastrointestinal lesions	4 of each
6. Purpura (gold) and embolism	1 of each

The three patients succumbing to heart disease of unknown cause will be described in detail in a subsequent report. In each instance the clinical and pathological findings relating to the articulations were those of rheumatoid arthritis. The exact cause of the cardiac lesions could not be determined. It is hoped that further study of these and similar cases may aid in ascertaining whether the heart changes represent an unusual manifestation of rheumatoid arthritis, are related in some manner to rheumatic fever, or are associated with a coincidental disease.

Subcutaneous Nodules. It is of interest that in both rheumatic fever and rheumatoid arthritis, subcutaneous nodules appear in approximately 20 per cent of the cases. In a previous communication (1940) it was pointed out that the subcutaneous nodules of these two diseases could usually be distinguished from one another. Study of an additional 24 nodules from rheumatoid arthritis patients and 23 from rheumatic fever subjects has further assured us that such differentiation is usually possible. It is believed that among the various tissue changes of rheumatoid arthritis, the subcutaneous nodule, when present, constitutes the most characteristic single lesion.

Conclusion. It is apparent that the usual anatomical changes observed in rheumatoid arthritis differ so markedly from those of rheumatic fever that one must infer that the pathogenesis of the observed lesions is different. Therefore, in the absence of etiological evidence to the contrary it would seem advisable to continue to look upon rheumatic fever and rheumatoid arthritis as separate and distinct entities.

RHEUMATIC HEART DISEASE IN AUTOPSIED CASES OF RHEUMATOID ARTHRITIS

(Abstract)

By THEODORE B. BAYLES, M.D., *Boston, Massachusetts*

OF 23 autopsied cases of rheumatoid arthritis six were found to have changes in both the heart valve leaflets and the myocardium similar to those that usually follow rheumatic fever. The histologic lesions of one of these six could possibly be considered active and five were inactive in character. Excluding one patient because of definite rheumatic fever and rheumatic heart disease in childhood, 22 per cent had rheumatic cardiac lesions. The factors of accentuation on cardiac death, the relatively large group with cardiac changes antemortem as compared to control groups, and the small number of cases (possibly one) with active rheumatic fever lesions have been pointed out. · No patient who had histologic evidence of rheumatic fever failed to show evidence of this on gross examination. A coincidence, a relationship between rheumatic fever and rheumatoid arthritis or the possibility that the heart disease is related to rheumatoid arthritis might be

inferred from these data. Since patients with rheumatoid arthritis have to die of some other cause than their disease, we wish, as yet, to delay a final conclusion until further studies teach us which one of the above three situations truly obtains. In the clinical treatment of these patients, we have preferred to consider the cardiac changes a coincidence of rheumatic heart disease and rheumatoid arthritis.

THE CAUSE OF DEATH IN THIRTY CASES OF RHEUMATOID ARTHRITIS

(Abstract)

By EDWARD F. ROSENBERG, *Chicago, Illinois*, ARCHIE H. BAGGENSTOSS, and PHILIP S. HENCH, *Rochester, Minnesota*

WE have studied the cause of death in 30 cases of rheumatoid arthritis. This number represents all the cases of this condition in which necropsy has been performed at the Mayo Clinic in the past 25 years.

In each case the arthritis had been progressive and had produced some degree of crippling. The articular changes were easily detected and included spindle shaped swellings of joints, atrophy of muscles, synovial thickening and effusions, and some degree of fibrous ankylosis. In a few early cases roentgenograms were negative, but in most of the cases the roentgenograms showed swellings of soft tissues, osteoporosis, varying degrees of destruction of cartilage and bone, narrowing of joint spaces, and sometimes marginal lipping. Constitutional reactions were commonly present.

A history of rheumatic fever was obtained from only two of the 30 patients. The ages of the patients at time of death ranged from nine to 77 years; the majority were in the third to the sixth decade of life. The series included 17 males and 13 females.

Cardiac lesions indistinguishable from those of rheumatic heart disease were found in 16 cases; seven of these proved fatal. Nonrheumatic heart disease was present in eight cases and proved fatal in two cases. Coronary occlusion caused the death in one of these cases; myocardial degeneration of an unknown cause in the other.

Eleven patients died of pulmonary disease, including bronchiectasis with diffuse pulmonary suppuration, pulmonary embolism, bronchopneumonia, pulmonary fat embolism, and massive collapse of the lungs.

Three patients died of renal disease; two from acute pyelonephritis with anuria and one from severe amyloidosis. Two patients died after long continued diarrhea of an unknown origin.

In five cases deaths resulted from miscellaneous causes including cinchophen hepatitis, accidental violence, carcinoma, sudden death during surgical anesthesia, and in one case the manner of death was unknown.

The causes of death can be classified into three groups. In the first group the fatalities were not in any way related to the arthritis, deaths being due to coronary occlusion, pulmonary suppuration, accidental death and death from carcinoma. In the second group, deaths resulted from some form of therapy undertaken for the arthritis, for example, deaths from reactions to typhoid vaccine, from cinchophen hepatitis, fat embolism following manipulations of joints and pulmonary embolism following applications of casts. In the third group the deaths appear to have resulted from visceral diseases which probably represented a part of the rheumatoid disease, for example, rheumatic heart disease, amyloid degeneration, or prolonged exhausting diarrhea.

Discussion on papers of Dr. Bennett; Dr. Bayles; Dr. Rosenberg et al.

Dr. CURRIER McEWEN, New York City: Dr. Hench has mentioned that our Society tends to be made up of two groups: those interested primarily in chronic arthritis and those concerned with rheumatic fever. Today's program, however, gives striking proof of the value of studying the rheumatic diseases as a whole. I, for one, feel that these three papers which we have just heard on the pathologic changes in the heart in the two diseases have made this one of the most profitable meetings I have attended. My first comment is one of admiration for all of those who have been able to get together so many necropsies on patients with rheumatoid arthritis. From personal experience I know how difficult it is and what a careful follow-up it entails. Dr. Bennett's presentation of the pathologic findings and the slides were a treat for all of us. I would like to ask him whether in the course of his examination of the tissues he came on anything that might throw light on the controversial question of fibrositis? Aside from the changes in tendon sheaths and joints was there inflammation in other supporting fibrous tissue such as tendons or fascia or in the muscles?

There are a good many who believe that rheumatic fever and rheumatoid arthritis are closely related, and the similarity of the subcutaneous nodules occurring in the two diseases is one of the strong arguments usually advanced in favor of that view. Dr. Bennett's pathologic observations cast doubt on the validity of that argument for he finds the nodules different. I am still of the opinion, however, that the differences he has pointed out are explainable on the basis of the differences in age and size of the nodules in rheumatic fever and rheumatoid arthritis.

Dr. M. H. DAWSON, New York City: I think the papers which have been presented speak for themselves. What is needed in this study is further information, and such information is gradually being assembled. I would like to ask Dr. Bennett what the underlying lesion was in the three cases of subacute bacterial endocarditis, particularly if there was underlying rheumatic disease. I have always felt that the nodule from a classical case of rheumatoid arthritis was quite different from that seen in a classical case of rheumatic fever. However, I would like to reaffirm my belief that all intermediate stages occur. If one studies nodules which have persisted for many months in rheumatic fever one will find them surprisingly similar to nodules of corresponding duration in rheumatoid arthritis. Conversely, if one studies an early and acute lesion in a fulminating case of rheumatoid arthritis, and such do occasionally occur, one is impressed with the similarity which they show to the nodules of rheumatic fever. Finally in such a comparative study one should be sure that one is comparing tissue from individuals in the same decade of life.

In evaluating the frequency of rheumatic hearts in rheumatoid arthritis, I believe that all the alternatives Dr. Rosenberg spoke of must be considered. In particular, much depends upon the type of material one studies. At the Research Hospital for Chronic Diseases on Welfare Island, Dr. Steiner examined 40 rheumatoid arthritis patients very carefully for evidence of rheumatic heart disease. Thirty-five per cent were found to be so affected. Now I do not suggest that 35 per cent of all patients with rheumatoid arthritis have rheumatic hearts but such was the case in a limited series carefully studied. In a few instances the electrocardiographic changes were minimal and could not have been detected had not frequent tracings been made.

Finally, one cannot refrain from commenting upon the *immediate* cause of death in many of the cases reported here today. One notes deaths attributed to cinchophen, typhoid vaccine, foreign protein therapy, and to manipulations. Such a record is not a happy one, but it will at least serve to remind those who consider gold salts too dangerous that other therapeutic measures are also not without danger in this disease.

Dr. D. M. ANGEVINE, Wilmington, Delaware: I wish to express my admiration of the technical excellence of Dr. Bennett's presentation.

Dr. Bennett mentioned that the presence of clusters of lymphocytes in long standing cases might indicate "activity." Such focal accumulations of lymphocytes are seen fairly frequently in sites such as the renal pelvis, or urinary bladder and although they probably indicate some previous infection one does not usually associate such an observation with active inflammation.

The muscle studies were of considerable interest and it is to be hoped that they will be continued. I am in complete accord with the statement that rheumatoid arthritis and rheumatic fever should be considered as separate entities. I should like to ask Dr. Bennett two questions: (1) Were any pathological changes noted in serous cavities other than those described in the pericardial sac? (2) How frequently was amyloid disease observed in this series of cases?

Dr. Bayles included cases of Strümpell-Marie spondylitis and Still's disease in his series of cases. Although these conditions should rightly be considered as rheumatoid arthritis it would seem best in an anatomical study of this nature to make some separation especially where there are so few cases in the series. It also would be preferable not to mention a "questionable Aschoff body." Many such lesions are confusing but the pathologist should state that in his opinion the lesion is or is not an Aschoff body. Of course there will be a great deal of variation among pathologists.

With the criteria that Dr. Rosenberg has set up for the diagnosis of rheumatic heart disease it is difficult to see how he could avoid making such a diagnosis on any heart. With our present state of knowledge it is difficult to know exactly what significance to attach to calcification of the aortic valve.

Dr. B. LEICHTENTRITT, Eloise, Michigan: The peripheral nerves of eight autopsied cases of typical rheumatoid arthritis were examined by Drs. H. A. Freund, G. Steiner, A. E. Price and myself. In seven cases small nodules were observed in the perineurium. We consider these lesions specific for rheumatoid arthritis and suggest the name rheumarthritic nodulous perineuritis.

The nodules were usually located in the perineurium, and rarely in the epineurium, but never in the endoneurium. When stained with hematoxylin-eosin the nodules are visible to the naked eye as bluish round or oval shaped lesions. The size of a single nodule varied between 0.14 and 0.2 mm. in diameter.

The microscopic appearance was characteristic, showing three different zones: first, a lymphocytic and plasma cell peripheral ring; next, a middle zone of polyhedral cells with large irregular nuclei poor in chromatin, comparable to the epithelioid cells of other granulomatous tissues; and third, an innermost pale and acellular

center with homogenously staining masses in which are occasionally embedded small dark granules of nuclear debris.

There are some variations of the layers: the acellular center may be missing, the inner zone may contain a central blood vessel, or the intermediate zone may be represented only by a few epithelioid cells.

As a control we studied more than 100 cases of various nonarthritic diseases and in no instance were similar lesions found.

Because these lesions were found in seven of the eight cases examined, because of the regularity with which they occur in the perineurium or near the epineurium, and because of their sharply circumscribed nodular character, we believe these lesions of the peripheral nerves are a specific pathological feature of rheumatoid arthritis.

DR. HUGO A. FREUND, Detroit, Michigan: I have been convinced for many years of the likelihood of a nervous system involvement in rheumatoid arthritis. The pain along the course of the nerves, sweating, glossy skin, interosseous muscle atrophy, hyperactive reflexes, and numerous other lesser changes could be explained only on the basis of nerve, ganglion, or spinal cord involvement. Dr. Alvin E. Price and I have studied cases clinically for many years. We have been able, with the assistance of Dr. Bruno Leichtentritt, and Dr. Gabriel Steiner; to show that nodules of specific character are found in the perineurium of the peripheral nerve. Dr. Leichtentritt has just described these nodules. They have not been found in controlled cases, and appear to be specific in rheumatoid or atrophic arthritis. Clinically, these findings explain many of the signs and symptoms of the disease.

DR. WALTER BAUER, Boston, Massachusetts: In reviewing our series, Dr. L. Raymond Morrison found eight cases that showed peripheral nerve changes similar to those described by Dr. Steiner. Other changes were noted in the spinal cord; these will be reported at a later date.

DR. CHARLEY J. SMYTH, Eloise, Michigan: I would like to add a few remarks concerning 10 patients seen at Eloise, Michigan. All were unquestionably cases of rheumatoid arthritis. As far as could be determined 50 per cent had both gross and microscopic lesions of rheumatic heart disease.

With relation to Dr. Leichtentritt's comments regarding the peripheral nerves, in four of the five cases in whom peripheral nerves were studied, findings compatible with rheumatic heart disease were observed. Two of these 10 patients died from myocardial infarction. In no instance was the diagnosis of rheumatic heart disease established during life.

The occurrence of this high percentage of lesions characteristic of rheumatic heart disease is strong evidence to indicate that rheumatoid arthritis and rheumatic fever are related.

DR. GRANVILLE A. BENNETT, Boston, Massachusetts (closing): Dr. McEwen has inquired about the pathology of fibrositis. Our material from cases of this disorder is small and I do not feel justified in attempting to interpret such lesions as have been observed.

In reply to the comments of Drs. McEwen and Dawson on the similarity of the subcutaneous nodules of rheumatic fever and rheumatoid arthritis, I wish to acknowledge the general morphological resemblances of these lesions. On morphological grounds, however, taking all cases in our series as they have come, it usually has been possible to distinguish between these particular lesions.

The cases of bacterial endocarditis about which Dr. Dawson inquires are noted on a short table in which the cardiac lesions of the 48 autopsied cases of rheumatoid arthritis have been tabulated. Twenty-four patients showed pathological changes in the heart and pericardium. These lesions were interpreted as follows:

(*a*) Probably rheumatic heart disease—seven cases. In these cases there were valvular lesions that appeared to have resulted from rheumatic endocarditis.
(*b*) Possibly rheumatic heart disease—three cases. (In two of these there were bacterial vegetations upon deformed valves.)
(*c*) Pericarditis or pericardial scarring of unknown etiology—three cases.
(*d*) Carditis and aortitis of unknown etiology—three cases. (A terminal hemolytic streptococcus bacteremia was present in one of these patients.)
(*e*) Heart lesions unrelated to rheumatic fever—eight cases.

No Aschoff nodules were observed in any of these 24 cases.

Dr. Angevine has commented on the lymphocytic infiltration of the synovial tissues. I have considered the presence of such infiltrations to be an indication of continued activity of the rheumatoid arthritis process. Such a cellular response can best be explained as a reaction to some form of local tissue injury. I cannot answer Dr. Angevine's question concerning the frequency with which the various serous cavities have been affected. Eleven of our cases showed amyloid infiltration. Nephritis was present in seven instances. Of these there were four cases classified as glomerular nephritis.

Dr. Leichtentritt's findings with regard to peripheral nerve lesions in patients with rheumatoid arthritis promise to be of considerable interest. Our material will be investigated with these observations in mind.

DR. E. F. ROSENBERG, Chicago, Illinois (closing): Dr. Angevine has raised the question as to whether the lesions I have shown in the hearts were really lesions of rheumatic fever. In answer, I wish to say that we have studied them carefully and we are personally convinced that the lesions are indistinguishable from the lesions of classic rheumatic heart disease. Furthermore, we have not been satisfied to rely on our own impressions concerning this important point, and, therefore, submitted the specimens to Dr. H. E. Robertson of the Department of Pathology of the Mayo Clinic, and also to Dr. B. J. Clawson, of the Department of Pathology of the University of Minnesota. Both of these experienced pathologists have agreed independently that the specimens do show the lesions of rheumatic heart disease.

THE PRESIDENT'S ADDRESS

LORING T. SWAIM, M.D., *Boston, Massachusetts*

Ninth Annual Meeting of the American Rheumatism Association,
June 8, 1942, Atlantic City, New Jersey

The conditions of total war have no precedent. The medical profession has responded magnificently with bold and novel remedies until recently unheard of. Total war is also waged against the courage and spirit of man. Therefore, a new morale is demanded as an important factor for victory.

The medical profession is always pioneering into the unknown fearlessly and unselfishly. Doctors have the good of the community at heart and the spirit of the Good Samaritan as a way of life, so that the goal I am pointing out for medicine is consistent and logical.

Total victory calls for unheard of human sacrifice. It calls for a supreme state of fitness, physically, mentally and spiritually, the extra plus in

living and in inspired thinking.   The medical profession *can* and *must* play a major rôle in the attainment of that total national fitness.

The profession must look to the future.   We have an important part in equipping the American people for that great job of reconstruction in the critical post-war years.

Never before have civilians been forced to suffer in the same way as is happening on such a huge scale in the world.   The post-war period will bring unique problems of adjustment, one of which will be finding the way to free people from bitterness and hate.

The challenge to medicine is not only to cure the bodies but to find the spiritual answer to these emotions and lay the foundations for curing a diseased and maimed world.

Doctors have pioneered in medicine.   Why should we not pioneer into the great intriguing soul in man which is spiritually ill, and heal it?   Dr. Steinmetz has predicted that the next important discoveries will be along spiritual lines.   America can be the nation, the pioneer, to give that necessary new thinking and living to the world.   Because of experiments with arthritic patients I am convinced that these predictions can be realized.   A simple plan is suggested by the following experiences.

Rheumatoid arthritis is a constitutional disease.   Since the disease affects all parts of the individual, to get the best results we must treat the whole individual, not only his body and mind but his *soul*.   We have made great strides in the medical care of rheumatoid arthritis, in diet, rest, gold salts and medicines, and building body resistance.   Deformities can be prevented by orthopedic care.   Surgery is able to restore deformed joints to comparative usefulness.   These are all essential in the treatment.   Yet evidence accumulates that physical health is closely related to spiritual health.   No constitutional disease is free from the effects of mental states.   Rheumatoid arthritis is no exception.

The effect of emotional upsets can no longer be considered mere coincidence.   My investigations in the last 10 years show that anxiety and resentment are the two most constant emotional reactions in rheumatoid arthritis, and maladjusted human relationships are a real problem.

Why are resentments and fears the most common reactions?   What fault of character has been developed?   What quality of heart is lacking? The selfish character is usually fearful, worrying, resentful and easily angered; the unselfish character is loving, fearless, forgiving in its attitude. This is true in my series of 171 cases.   The question is how to change individual character so that there is no selfishness.   We cannot of ourselves change the quality of our spirit.   What we really want is a new spirit in man, new motives of friendship, patriotism and world outlook, a new philosophy for living.

There are spiritual laws which will change lives if they are scientifically applied and a new spirit results.   The patients I have studied make me

believe that all forms of selfishness point to a starved, undeveloped spiritual life. The spiritual life needs to be nurtured to develop an unselfish character.

A plan has evolved for feeding a starved spirit. Besides the medical history questions are asked about intimate relationships with members of his family, friends, and in business. It is essential to help people see their own failings of disposition, and rectify their own mistakes. With friendly confidence people instinctively tell the truth about their resentments and fears.

Next explore the personal beliefs or set of standards by which the person actually lives. Find out if his beliefs affect his thinking and actions or are purely intellectual, for on these foundations we must build as stepping stones to further growth. Day by day by explaining and teaching the spiritual laws of the Bible, by times of directed reading and thinking along lines of conduct such as honesty, unselfish living, care for others, the patients grow in understanding. People do not know how to be honest and are blind to their motives.

For example, without any physical reason a woman in the hospital began to vomit every morning after breakfast. She was full of self-pity and resentment against others in her ward who had visitors while she had none. She was blind to her jealousy but when she realized her self-absorption she repented and apologized, and thus restored friendly relations with her neighbors. This cured her resentments and her illness. Her whole life was changed by the application of this simple principle of repentance and apology as an answer to resentments, for her life was a series of resentments at home.

Let me illustrate what happens to character when this sort of spiritual education is carried out. A woman of 32 who had had an unhappy marriage obtained a divorce. Through propinquity and lack of funds she drifted into certain unfortunate relationships, making her dependent and helpless. Her vitality was lowered by constant fear and resentment. Typical rheumatoid arthritis developed. She was unable to walk for six months. Her relationships were all wrong. Her early religious belief was weak and almost gone from neglect. Daily Bible study, reading and thinking were started. Her spiritual life grew. Because of the change in her she found work, married again, and is now doing all her own housework. The most remarkable change has been in her emotional reactions to life which are now outgoing, unselfish and fearless. A new faith, hope and caring for people have completely changed her earlier way of life, have given her courage to face the previous defeats and not succumb, to stand up to those who have tried to pull her back to the old life. She has really found a victorious life. She has an unwavering faith in God and His direction. The old reactions no longer occur. She knows the value of spiritual health and sets aside time for it each day. Her joints improved. Now her arthritis is inactive. I cannot say that she recovered from her arthritis because of the development of her spirit, but it was an essential factor in her final recovery.

A man at the age of 50 came for the treatment of rheumatoid arthritis. His weight was down from 175 to 149 pounds. His relationship history showed a deeply rooted resentment of many years' standing associated with people in his work and his home relationships were strained. Although entirely successful in business he had a sense of complete failure about his whole life. He had only an inherited belief which was undeveloped and superficial, in no way affecting his thinking or life.

He faced facts and made a new start. He began spiritual training. During the first year there was a complete change in this man's physical health. He gained 30 pounds. The rheumatoid condition cleared up. His emotional outlook has changed, old resentments have been cleared up by apology; the whole family relationship is different. In the last nine years his spiritual foundations have been so firmly laid that they are the basis for his conduct. A new spirit has come in his job and he is helping many of his associates, for when people find this new experience the best way to keep it fresh and vital is to help others.

There are many patients who came for arthritis and really were spiritually starved and who through feeding their spiritual lives have found that their whole personalities were changed. There is very little conception of these great spiritual forces. People do grow and their lives deepen as they develop a personal relationship with God. This superforce is the crux of the change.

The spiritual approach does not cure the arthritis, but it is an essential factor, a factor without which the patient cannot advance beyond a certain point. It has a very definite place in "complete treatment." It makes people live victoriously. If "complete treatment" could be instituted early there would be very many fewer cripples, and if people would cultivate a mature, developed faith and belief in a superforce as part of their character they would never react with fear and anger the way they do under emotional strain. This "complete treatment" is no longer an experiment with me, but medical success or failure in many cases depends on this spiritual factor.

Consider the situation of our nation, and our responsibility for building the future world order. The world is sick today because nations have been starved exactly the way these patients have been starved. The nations have not learned to live together any more harmoniously than these patients have. The remedy is the same, i.e., to feed the spiritual lives of nations through individuals. The world to be must have this new spirit. In the passing world selfishness prevails. If this quality is carried over, the world will be actually in essence the same. A new order requires a new spirit.

Doctors are admittedly leaders. Shall we pioneer again and seek this new spirit for ourselves that we may guide our nation and the world to the highest spiritually? "The trouble with nations is human relations, especially you and me." A determined minority could remake the world. Shall we lead the way to bring about the greatest revolution in all time, the revolution in the hearts of men?

FOOD ALLERGY AS A POSSIBLE FACTOR IN SUBACUTE RECURRENT ARTHRITIS

(Abstract)

By WARREN T. VAUGHAN, M.D., *Richmond, Virginia*

IN a consecutive series of 1000 adults complaining primarily of allergy (asthma, hay fever, urticaria, migraine and allergic dermatitis and indigestion), 27 had recurrent subacute involvement of various joints. The allergic etiology in these 27 cases was indicated either by the fact that the causative foods were discovered and the attacks prevented by their avoidance, or that, although the etiologic foods were not discovered, the joint manifestations appeared synchronously with other allergic symptoms and were relieved with improvement in the latter.

Thirty-two foods were incriminated. Strawberry and tomato, the "hearsay" foods customarily suspected in rheumatism, were relatively unimportant in this list.

Four had intermittent hydroarthrosis. One had intermittent hydroarthrosis superimposed on chronic rheumatoid arthritis. Thirteen showed predilection to involvement of the small joints with symptoms resembling rheumatoid arthritis. In some, the joint symptoms were intermittent, in others, they were chronic with exacerbations. In the former one must consider a condition similar to intermittent hydroarthrosis with predilection for small joints, whereas in the latter one must consider true chronic arthritis with exacerbations caused by allergenic foods. Those with negative physical findings at the time of examination may belong in the group with intermittent hydroarthrosis of large or small joints. Detailed illustrative case histories are given.

This series is compared with Kahlmeter's 54 cases attributed to allergy, among approximately 5,000 rheumatics; Solis-Cohen's 27 cases observed in 20 years in whom allergy may have played a part, and Hench and Rosenberg's 34 cases of recurrent or palindromic rheumatism.

In the author's series all patients were allergic to foods, although in two instances inhalant allergens appeared to play exciting rôles.

Although food allergy has not been proved to play a part in the majority of arthritics, there appears to be a small group in whom intermittent hydroarthrosis involving large joints or multiple small joints (with a picture of recurrent subacute rheumatoid arthritis) may be caused by food allergens. This may occur in persons whose joints are normal between attacks or may appear as an exacerbation in persons with chronic arthritis, presumably not caused by food allergy. It may occur in osteoarthritis, rheumatoid arthritis, or combined arthritis, but in all cases, when small joints are involved, the picture is "rheumatoid."

Discussion on paper of Dr. Vaughan, "Food Allergy as a Possible Factor in Subacute Recurrent Arthritis"

DR. RALPH PEMBERTON, Philadelphia, Pennsylvania: This paper by Dr. Vaughan is timely. Fifteen years ago Dr. Harry Wilmer studied with me a series of cases at the Presbyterian Hospital in Philadelphia but our results were negative. About eight years ago another series of cases was studied with Dr. Wilmer and Dr. Merle Miller but the results were again negative. The positive results reported by Dr. Vaughan, however, may have more significance. About eight years ago there appeared a paper from the Central Institute of Public Nutrition in Moscow by Pevsner et al. in which these authors reported a series of cases which they believed to have been benefited by restrictions of diet. They related this benefit to a form of desensitization.

Many of us have been increasingly impressed by the value of rest and sedation of the nervous system in the treatment of arthritis. Allergic reactions involve the nervous system and it is possible that some of the benefit in the favorable cases reported derive in part from this premise. Only recently two physicians whose symptoms cleared up satisfactorily on the basis of rest and mild sedation, told me that they would not have believed without experience that their arthritic symptoms could be made to subside so easily. There is obviously a need for further observation of these angles of the arthritic problem and I hope that Dr. Vaughan will continue his studies.

DR. RUSSELL L. CECIL, New York City: I am very glad Dr. Vaughan has made this study and I hope he will continue it, because it is along a line that has been rather neglected in the study of arthritis. We are all familiar with the studies made by Swift and Klinge, both of whom pointed out certain similarities between the lesions of rheumatic fever and arthritis and those of hyperergy both in human and animal experiments. Dr. Swift noted a similarity between joint lesions in serum sickness and rheumatic fever. When you think about it, it is surprising that we do not see reactions of hyperergy more often in joints than we do. Klinge's experiments always interested me, namely, hyperergy produced in the joints of animals by the injection of serum or albumin. If arthritis is an expression of an allergic state in the joint no one has yet indicated what form of allergy it is. As Dr. Vaughan suggests, it is probably not an inhalant, possibly a food, possibly bacteria.

A few years ago Dr. Wainwright gave an interesting report before this Society on streptococcal skin tests and used streptococci which had been recovered from patients with rheumatoid arthritis for vaccine therapy. The criticism made at that time has been heard since, namely, that so many normal individuals have positive skin reactions to streptococci and other bacteria that positive reactions in an arthritis have very little significance. When we come to consider the different forms of arthritis in relation to allergy, the problem is even more difficult. We have patients who tell us they have pains in their joints and that after eating certain foods, the pain is increased. However, in going back over my personal experience, I have great difficulty in recalling any case in which there was actually a connection between food and swelling. I recall a case years ago of a young women who came to the Cornell Clinic with typical rheumatoid arthritis. She felt that food had something to do with it. We tried putting her on a fast for a week, with nothing but water and weak tea. She stuck to the fast very faithfully. She came in at the end of the week with a remarkable improvement. She went into a typical remission, and gradually went back to her original diet. The unfortunate part of the story was that later on she had a recurrence and when the fast was repeated no benefit was obtained.

As far as hypertrophic arthritis is concerned, I cannot feel that allergy has anything to do with it. Pemberton made studies on carbohydrate metabolism in patients with osteoarthritis and felt that these patients were helped by a low carbohydrate diet. Acute gout is often claimed to be a form of allergy, but that has to be proved. It

seems to me we make a mistake in placing too much emphasis on what patients state. We all get joint pains, not so much from food as from alcohol in various forms. Certainly some of the heavy wines are conducive to a feeling of stiffness which could not be called gout but possibly a fibrositic form of rheumatism. We have to bear in mind that allergy and arthritis are both common; some forms of allergy are extremely common and we have to allow for a certain amount of coincidence in these two conditions.

I cannot say very much about palindromic arthritis though it certainly bears some resemblance to an allergic condition. I would like to ask Dr. Vaughan to say a word more about the second case in the series of patients he described.

Dr. Francis C. Hall, Boston, Massachusetts: We have been interested for 20 years in the possibility that food allergy is a factor in arthritis. Dr. George Minot raised this question about that time, pointing out that there was some evidence suggesting that people with arthritis were particularly subject to allergies of various kinds, and had family histories of allergy. Therefore, we have had allergy in mind over the years, and have looked into the matter when taking histories.

We have not found food allergies common in people complaining of joint disturbances. Every once in a while one sees a person who has skin allergy, or asthma, and swelling of the joints associated with the eating of some food. Usually the patient has determined this relationship, however, and these joint swellings are of a very transient nature if the patient omits the offending food.

One of our leading allergists in Boston, Dr. Francis Rackemann, has made the statement that of all the patients that he sees come into his office with various types of allergy, patients with arthritis are conspicuously absent. We have rarely found allergy present in patients with either of the two main types of chronic arthritis, though in addition to looking for it in the record, we have intermittently done skin tests.

Dr. A. S. Gordon, Brooklyn, N. Y.: I would like to ask Dr. Vaughan in reference to his group of cases, what were the eosinophile counts, and the sedimentation rates; and did he succeed in obtaining passive transfers in these cases?

Dr. Warren T. Vaughan, Richmond, Virginia: Several years ago a patient said that strawberries and tomatoes caused her rheumatism. Doctors are as much at fault as the laity in suggesting that strawberries and tomatoes cause rheumatism. To our surprise we found that she was allergic to these two foods. She improved on avoidance. Then we started testing all rheumatics with foods but gave up after 25 patients, because we were getting nowhere. My interest was drawn back to this recently in this series of patients with the picture of intermittent arthritis involving small joints. I found cases in which non-allergic chronic rheumatic involvement was accentuated by food allergens. I would emphasize the infrequency of the condition rather than its frequency.

We do know that joint involvement may be a part of an allergic reaction as we see it in serum disease.

As far as the eosinophile count, sedimentation rate and passive transfer are concerned, I cannot give you any information from my studies. Studies of passive transfer and eosinophila would be of little benefit since they are notoriously inconstant in food allergy, but the sedimentation rate might enable us to discriminate between allergic reactions and exacerbations due to infection.

RHEUMATOID SPONDYLITIS AS A CAUSE OF INCREASED CEREBROSPINAL FLUID PROTEIN. BASED ON THE STUDY OF 101 PATIENTS WITH RHEUMATOID ARTHRITIS

By ALFRED O. LUDWIG, M.D., CHARLES L. SHORT, M.D., and WALTER BAUER, M.D., *Boston, Massachusetts*

THE neurologic manifestations of rheumatoid arthritis are numerous, extremely variable and at times so striking as to simulate disease of the central or peripheral nervous system.   An analysis of these clinical features in 293 unselected consecutive patients with rheumatoid arthritis and the results of detailed neuropathological studies are in progress.   The present report deals only with the cerebrospinal fluid findings in this disease.

The cerebrospinal fluids examined during the course of this study were obtained from 101 patients with rheumatoid arthritis, 59 of whom suffered from peripheral joint disease alone and 42 from spondylitis with or without peripheral joint involvement.   Cerebrospinal fluid analyses were repeated in 11 instances (seven patients with and four without spondylitis).

The only significant abnormalities observed were increased total protein, abnormal colloidal gold curves or a combination of the two.   The fact that 15 of the 16 patients with increased spinal fluid protein had either spondylitis or symptoms suggesting spinal involvement strongly suggests a relationship between an elevation of the spinal fluid protein and the presence of rheumatoid arthritis in the spinal and sacroiliac articulations.   Such alterations occurred more frequently in the spondylitis patients with severe pain or sciatica or both and hence presumably a higher degree of inflammatory activity.   Factors probably involved in the production of these abnormalities are alterations in the serum proteins and increased permeability of the meninges because of their proximity to the inflamed articular tissue.

TREATMENT OF TWO HUNDRED CASES OF CHRONIC ARTHRITIS WITH MASSIVE DOSES OF VITAMIN D PREPARED BY THE WHITTIER METHOD

By R. GARFIELD SNYDER, M.D., WILLARD HAYWOOD SQUIRES, M.D., JOHN WILFRID FORSTER, M.D., and CORNELIUS HORACE TRAEGER, M.D., *New York, N. Y.*

THIS study was to determine (1) the toxicity and (2) the therapeutic value of treatment with massive doses of vitamin D.   The dosage used varied from 100,000 to 500,000 units daily.   The average dose was 200,000 to 300,000 units.   Within the limits of this dosage, in over five years, no deaths occurred and no evidence of serious toxicity was observed.   No definite increase in the calcification of the blood vessels, as proved by roent-

genograms, occurred, nor were there any evidences of stone formations in the kidney or gall-bladder or recalcification of bones. A few cases developed mild toxic symptoms such as nausea with occasional vomiting, but they were easily controlled by stopping the medication for a few days. In a few cases moderate hypercalcemia was noted, but was easily controlled by reduction or complete cessation of the medication for a few days.

The authors presented a moving picture of five patients before, during and one year subsequent to the institution of treatment.

The results in the last series of 50 cases were as follows: 7—excellent, 20—good, 8—fair, 9—slight improvement, and 6—failures. The percentage of excellent results is not high, but the cases were especially selected as a severe test for this new method of treatment. With rare exception, all were of over two years' duration, and more than half had had arthritis for some five to 25 years. The few patients selected who had had the disease for less than two years were chosen solely because the rapid downward progress of the disease made them a severe test for any form of treatment. To eliminate the possibility of spontaneous exacerbations and remissions, the great majority of the patients in this series had been under observation for at least two years and had previously proved resistant to all tried forms of therapy.

Because there is no specific for chronic arthritis, any new form of treatment which promises a fair chance for improving a refractory case should be welcomed as an additional form of therapy, especially as it has been found that this medication is not harmful in the dosages employed. It apparently is not a specific, and it is not known how it acts, but this is equally true of the sulfonamides, salvarsan, gold, etc. Obviously it is a powerful tonic as the patients usually gain weight and feel better. It is believed that the improvement observed was not coincidental to the "burning out of the disease." It would be most improbable that such improvement would occur suddenly from natural causes. It should also be noted that following the cessation of treatment, the improvement was sustained for weeks and even months in a large percentage of cases.

EVALUATION OF ARTHRITIC CASES TREATED BY VITAMIN D

By Lewis Clark Wagner, M.D., *New York City*

When the research work on chronic arthritis was begun at the Hospital for Ruptured and Crippled with vitamin D therapy, it was considered best to have an impartial orthopedic surgeon evaluate the results of the cases under treatment. He was to have nothing to do with the general care and treatment of the patients, but examined each patient on his first visit to the clinic and reëxamined him at the end of one year.

These patients were examined very thoroughly, the examinations involving all the locomotive systems of the body. In general, each examination included the appearance of the patient and described his habitus, his method of walking if possible, and his activities. The loss or gain of weight was noted, as was the patient's normal size. All joints were tested as to range of motion and the major joints were measured. Deformities and swellings of the joints were tabulated. Muscle strengths were estimated and disabilities noted.

At the end of one year, these patients were seen again, and a separate, thorough examination was made. By comparing the two examinations, one was able to deduce whether there had been any improvement or not.

In the final evaluation of these cases it was necessary to have certain criteria from which to arrive at one's conclusions. These were as follows: (1) feels better; (2) increased weight; (3) loss of pain; (4) increased motion; (5) decreased joint swelling. It must be added that these patients probably could not get much worse, so we looked for positive findings. They were cases on whom many forms of therapy had been tried with no improvement.

In the tabulation of the results, we have five major headings (see chart 1). The end results are rated none, poor (1 to 25 per cent), fair (25 to 50 per cent), good (50 to 75 per cent) and excellent (75 to 100 per cent). In judging in which column a case should be placed in the tabulation of results, if there were negative findings to all the criteria as stated above, the case would be placed in the no improvement column. A poor result would be one in which perhaps two or three positive results appeared out of the five suggested ratings, such as feeling better and loss of pain. In the fair group, the result would be judged by the possibility of feeling better, increased weight and increased motion, with loss of pain. Of course this can only be relative, as motion may not have improved in all the joints, but there may have been more motion in the shoulders, fingers, neck or knees. In the group rating called good, 50 to 75 per cent, one would find positive improvement in all five criteria on evaluation, considering most important partial loss of joint swelling and increased range of motion. The gain of weight and subjective symptoms of pain and feeling better are all added. In the last group, we have the cases which are marked excellent, showing 75 to 100 per cent improvement and these patients have shown improvement in every respect. There are two cases which were completely relieved. However, they are left in the excellent group.

The conclusions drawn from these orthopedic examinations and evaluations of the patients treated by vitamin D show that the greatest improvement appeared in the patients with rheumatoid arthritis. One noteworthy finding was that there was considerable improvement in four cases of Marie-Strümpell arthritis. This improvement was in the muscles of the neck and shoulders. However, the changes in the spine were not improved because

ankylosis had taken place.   It might be considered that the improvement in the osteoarthritic patients was of no particular note.

This report is upon 42 cases examined out of the possible 50 which are reported from the clinical angle in Dr. Snyder's section of this paper.   The eight other cases to complete the series were not available and thus my statistics have to be based upon the cases examined.

CHART I

Classification Type of Arthritis	End Results				
	None	Poor 1–25%	Fair 25–50%	Good 50–75%	Excellent 75–100%
Osteoarthritis	3		2		
Rheumatoid arthritis	5	2	18	2	5
Marie-Strümpell arthritis			4		
Bursitis (chronic)	1				
Total	9	2	24	2	5
Per cent	21.42%	4.76%	57.12%	4.76%	11.90%

42 cases examined at one year intervals.   Deductions from findings such as

     (1)   feels better
     (2)   increased weight
     (3)   loss of pain
     (4)   increased motion
     (5)   loss of joint swelling.

Discussion on paper of Dr. Snyder et al., "The Treatment of Arthritis with an Agent Containing Massive Doses of Vitamin D"

DR. CHARLES A. RAGAN, JR., New York City: At the Arthritis Clinic of the Presbyterian Hospital, New York, we had 31 cases.   These patients were admittedly a difficult group of cases.   Most of them had had gold and had developed some manifestations of intoxication, so we could not give them gold.   One developed agranulocytosis.   Four had the disease for less than two years.   A woman of 27 had the disease for more than three years.   None of them had it for less than a year. The treatment was not so prolonged as in Dr. Snyder's cases.   We continued the drug only for four months in 11 patients, in eight patients for four to six months, and in 12 for more than six months.   We did serum-calcium determinations on these patients and found no elevation after treatment.   In nine there was an elevation above 11.9. Eighteen of the patients developed some toxic manifestations, usually nausea and vomiting, which promptly cleared after cessation of the treatment.

As far as improvement goes, we were struck by one feature of the drug, namely that seven of the patients felt very much better.   In only one patient could we see any objective signs of improvement.   Seven showed a significant drop in sedimentation rate; eight were promptly improved but the result was not very striking.   Sixteen showed no improvement at all.   One remained well after he stopped the drug.   The remainder relapsed immediately after the drug was discontinued.   In view of the

report from Hopkins regarding the use of irradiated ergosterol we are hesitant to continue the use of this medication.

Dr. Darrell C. Crain, Jr., Washington, D. C.: I wonder if some one might have a little influence with the publicity departments of the manufacturers of the products that are used. Many of us have been getting advertising from the manufacturers of concentrated vitamin D which could be described as "enthusiastic," to put it mildly. Some well controlled experiments by other investigators would seem to indicate that concentrated vitamin D is not the super cure for rheumatoid arthritis that some are claiming. Certainly the general practitioner who gets some of the advertising put out by the Ertron Company might be led astray if he were to take it seriously. I think in all fairness to the medical men throughout the country Dr. Snyder might suggest to this company that it be a little more objective in its advertising.

Dr. Clyde Hartzell Kelchner, Allentown, Pennsylvania: Last April I enjoyed the privilege of seeing some of these patients whom Dr. Snyder was treating with Ertron. They were very much more enthusiastic about Ertron than were our patients at the Abington Memorial Hospital Arthritis Clinic. There was also some difference in the type of patient as well as in the type of treatment used in the two clinics. Dr. Snyder's patients were entirely pay patients, whereas ours were charity patients with a lower economic status. Ertron was the only treatment given his patients, but our group received rest, dietetic and physical therapy as well as all the usual, accepted forms of antiarthritic treatment, in addition to Ertron. Their focal infections were cleared up conservatively and we tried to correct their anemia as well as any other derangement of their physiological processes.

In our small group of 40 cases under Ertron therapy for 12 to 24 months, we had 22.5 per cent who said that they were better, although the sedimentation rate of these atrophic arthritics had not returned to normal levels. Another 22.5 per cent said that although their arthritis was no better, they felt much stronger while they were taking Ertron; 30 per cent were no better; 15 per cent refused to continue with the Ertron therapy (three said it made their arthritis worse; one refused it because of severe anorexia and marked weight loss; a fifth complained of severe headaches; and a sixth of sharp abdominal pain). There were four patients, or 10 per cent, in whom we stopped it because we were afraid to continue the Ertron. One patient, a man of 42, developed a coronary occlusion which may not have been influenced in any way by the Ertron. Two other patients developed a marked leukopenia during the course of Ertron therapy, one of whom developed a peculiar skin lesion which the dermatologists thought might be caused by an allergic reaction. Another patient showed a rise in blood phosphorus to 13 and phosphatase to 24 and we were afraid to give her any more. In all fairness to the drug, I must say that all of our 40 cases were severely involved atrophic arthritics.

Dr. Richard H. Freyberg, Ann Arbor, Michigan: I have been interested in hearing these reports. For the last three years we have been studying the effects of various preparations of vitamin D administered in large doses, including the preparation Dr. Snyder reported on. Our results were not so good as Dr. Snyder's. We followed 36 patients with rheumatoid arthritis, for at least two years and some as long as three years. Those 36 patients were given 45 different courses of treatment. Only 14 patients were considered to have had subjective improvement. Some of these reported considerable improvement but had only slight subjective improvement. There were only six instances of objective improvement among these patients. In only 16 per cent of cases was there a reduction in the erythrocyte sedimentation rate. We felt that only in the minority of patients was there any evidence of improvement in the course of the disease. There were a number of instances of gastrointestinal

irritation with anorexia and vomiting due to the medicine. In eight patients significant hypercalcemia developed and in many instances this was accompanied by quite severe symptoms. So we are not very greatly impressed by the evidences of improvement.

We wished to see whether or not some of the improvement might be on a psychogenic basis. Through the courtesy of the manufacturers of one of the preparations employed, capsules containing a placebo were made. These placebo capsules were given some patients for approximately two months before administration of vitamin D. Some patients who had subjective improvement with the vitamin D had no improvement when the placebo was given. We concluded that in the majority of cases the symptomatic improvement, where it occurred, was not on a psychogenic basis.

At this time we feel that evidence of improvement from large doses of vitamin D as we employed it is rather slight and occurred in only a minority of the patients. One mistake that many physicians are apt to make is to rely upon a single drug for the treatment of arthritis, so that little or nothing else will be done for these patients. We feel that this preparation certainly should not be relied upon as a remedy which will alter the course of the disease; less than half of our patients had symptomatic improvement, and considerably fewer had any objective evidence of improvement.

DR. R. GARFIELD SNYDER, New York City (closing): My purpose in presenting this paper on the treatment of arthritis with an agent containing massive doses of vitamin D was not to emphasize the value of any one type of vitamin D, but rather it was an attempt to arouse renewed interest in the use of massive doses of vitamin D in the treatment of arthritis.

Although our entire experience has been limited to the study of one particular type of vitamin D, it is obvious that the entire subject needs careful study, not only in one clinic but in many clinics, and that in the future comparative studies should be made of the various types of vitamin D to determine which one, if any, is the most efficacious and least toxic.

In this study we only used one therapeutic agent. Although it is necessary to do this from a scientific standpoint, it is hardly fair to any therapeutic agent to use it alone, for most agents should be used in combination with other well known therapeutic agents in order to get the maximum beneficial effect.

It has been brought out here this afternoon that at Presbyterian Clinic, Abington Memorial Clinic and the University of Michigan Clinic various degrees of improvement were obtained; most of the observers claim that they did not see as good improvement as we reported in our series. The fact that different clinics obtained various percentages of clinical improvement is not of great importance, because many uncontrollable factors enter into the question of relative degree of improvement obtained in any one clinic. For example, Dr. Kelchner visited our clinic recently and observed a very distinct difference in the class of patients we were treating and those treated in his clinic. Our clinic is a pay clinic; the patients are intelligent and very coöperative, whereas the patients in the Abington Clinic are charity patients. In the University of Michigan clinic the patients come from long distances throughout the state, so that they cannot return for frequent careful observation.

There is no reason why the clinical improvement should be absolutely uniform with this therapeutic agent, any more than they are uniform with gold.

In regard to the subject now under discussion, it is possible that they did not obtain a large percentage of good results at Presbyterian because of the fact that they only had a small series and did not keep up the treatment long enough. We have found from experience that many cases do not start to improve until the second or third month after treatment is instituted.

In regard to the toxic results reported from Johns Hopkins, it should be noted that they had only two cases. The vitamin D product used in these two cases was

only 50 per cent calciferol, and the remaining 50 per cent was made up of toxic side products. In addition, the dosage used in these cases was 700,000 units per day, which is almost three times what we found to be safe in our clinic with a much less toxic product. It seems strange to me that this report should even be published in the Journal of the American Medical Association. Certainly, a series of two cases is obviously too small a series on which to base any reliable conclusions, especially as all the toxic symptoms cleared up within two days.

The moving picture demonstration was presented as a new method of establishing objective improvement in a series of arthritis cases treated by a new therapeutic method. In view of the skepticism which always is associated with the introduction of a new form of treatment, we feel that this method of establishing unquestionable visible evidence of improvement should be used more frequently in the future.

In conclusion, we admit that we do not know how this form of vitamin D acts, and we do not know that massive doses of vitamin D are really necessary in order to cure arthritis. At the present time we have no known way of estimating the amount of vitamin D that is actually absorbed, as there is no chemical method to determine how much vitamin D is eliminated in the feces and the urine. It may be possible that most of it passes through the intestines unchanged. For that reason we have had this product prepared in such a manner that we can inject intramuscularly, so that we will actually know in the future how much vitamin D it is necessary to inject in order to obtain therapeutic results in arthritis.

We also admit that we do not know from previous experience that this particular product is better and less toxic than the vitamin D preparations made by the ultraviolet method. During the coming year we intend to carry out a very careful comparative study of another series, using vitamin D prepared by the ultraviolet irradiation method.

TREATMENT OF ARTHRITIC CONTRACTURES OF THE KNEE

(Abstract)

By JOHN G. KUHNS, M.D., *Boston, Massachusetts*

DEFORMITIES at the knee are among the most disabling of deformities in chronic arthritis. Five hundred and eighty-six contractures at the knee (313 patients) were found in 1453 patients suffering from chronic arthritis on the Wards of the Robert B. Brigham Hospital. A contracture is defined as a relatively fixed shortening of a group of muscles and their ligaments. After it has been present several years it often leads to irreversible changes in the muscles. Flexion contractures of less than 10° were not included in this study since, as far as could be observed, little disturbance in function resulted from so mild a deformity at the knee joints.

Extension contractures were recorded only if the knee could not be flexed more than 10° from the fully extended position. This type of contracture was observed only when the knee was kept in extension for long periods of time during the active stage of the disease, or when much force had been used in correcting a previous flexion deformity.

All of the contractures except 11 followed involvement of the knee by atrophic arthritis. Eleven flexion contractures occurred as the result of

hypertrophic arthritis. Usually both knees were similarly involved in the same patient, but there were 40 patients with flexion contracture in one knee and no deformity in the other knee. The case histories of these patients suggested that local trauma played the major part in this involvement of one knee only.

In attempts to prevent and to correct these contractures of the knee, a program of treatment was evolved which has been modified as more effective methods have been found. In patients seen during the first six months of their arthritis, contractures could usually be prevented.

The most effective method of preventing contractures at the knee when arthritis was present was rest in full extension until the muscular spasm and pain had subsided. Walking was permitted when motion and weight-bearing did not lead to pain. If the period of rest was prolonged beyond two weeks, exercises were often necessary to maintain strength and control of muscles about the knee. Splinting of the knee in extension was required if there was a persistent tendency to flexion. Fixation was not continued longer than one week without examining the knee and permitting a little motion temporarily. Long fixation of the knee without motion tended to produce extensive muscular atrophy and a contracture in extension.

When a flexion contracture could not be corrected passively, an attempt was made to correct it by a series of plaster casts. With the fixation of a plaster cast the muscular spasm usually subsided and the knee could then be brought into more extension. The plaster cast was cut into an anterior and posterior half in two days and was removed for short periods to permit the application of heat and for exercises when these could be performed without pain. When 10 degrees or more of correction in the contracture had been obtained a new cast was applied. Contractures were usually corrected by this method in from one to three months. For persisting weakness of the muscles of the thigh a caliper was then worn when walking to maintain correction until the muscles became stronger.

The results of treatment are listed as good with a final result of less than 5° of contracture; fair with from 5 to 15° of contracture remaining; and poor when there were more than 15° of persisting contracture. Many of the contractures of long duration and of severe degree required surgical correction. There is no satisfactory method of determining the resistance of contractures at the first examination. One can tell whether plaster casts will be effective usually only after several weeks of trial.

This study showed:

1. Arthritic contractures at the knee can be prevented: (1) by rest, if weight-bearing causes pain; (2) by splinting the knee in full extension, if there is muscular spasm; and (3) by exercise, if there is muscular weakness and atrophy.

2. When flexion contractures cannot be corrected passively the best early method of correction is a series of plaster casts, each cast securing as much

extension as possible. Calipers and exercises are usually required after full correction in order to maintain it until muscular strength is regained.

3. Flexion contractures too resistant for plaster casts are corrected most easily by a posterior capsuloplasty. It leads to painless weight bearing if the articular surfaces are not destroyed.

4. Manipulation, wedging casts and traction are relatively ineffective procedures. Skeletal traction is of value only after operations which free the contracture and permit extension gradually or the correction of a subluxation.

5. Arthroplasty is the procedure of choice in ankylosis if motion is desired. In chronic arthritis the end results to date have rarely been good. Osteotomy is employed when a better position for weight bearing alone is desired.

Discussion on paper of Dr. Kuhns, "The Treatment of Arthritic Contractures of the Knee"

DR. FRANK D. DICKSON, Kansas City, Missouri: Dr. Kuhns has not been guilty of over-statement when he says that contractures of the knee constitute one of the serious after results of arthritis. Such contractures do lead to very serious incapacitating disability.

In his discussion Dr. Kuhns has very wisely differentiated between contractures of limited duration and those that have existed over a long period of time. In the former we are dealing with tissues which are still plastic and more or less readily corrected. In the latter we have to do with ligaments which are fibrosed, thickened, and unextensible so that they not only resist efforts at correction, but tend very definitely to reproduce deformity even though this has been corrected by one of the methods which Dr. Kuhns has enumerated.

In cases of acute arthritis our experience parallels that of Dr. Kuhns in the desirability of maintaining the limb in extension in a plaster splint until the acute symptoms have subsided. This requires a number of weeks, as a rule. Then after the acute stage has subsided, it is desirable to remove the extremity from the splint and exercise the joints very gently, applying hot fomentations before such movements are carried out.

In older cases with fixed contractures, we are dealing with a different problem entirely. Deformities in these cases must first be corrected and such correction maintained or they will recur. Although I would admit that often and perhaps generally in these older cases, correction can be secured by a series of corrective plaster splints, our experience with this method has not been so happy as to cause us to use it extensively. Our failures have been due perhaps to lack of patience on our part. We prefer to do a capsuloplasty in these older, resistant cases rather than to attempt correction either by traction or casts.

In our experience forced manipulation has been of no value in resistant contractures. It can only add to joint damage and usually results in ankylosis in extension. There is one exception to this: in mild flexion contractures in which the joint is quiescent, I believe in such cases wedge casts properly handled are highly effective.

I cannot agree with Dr. Kuhns when he says that traction is not an effective method of correcting contractures. Compound traction or Russell's contraction acts very well, particularly in young individuals. I believe its value should not be overlooked.

Osteotomy, we feel, has an unimportant place in the treatment of arthritis and contractures of the knee.

Arthrodesis is a very useful procedure in badly damaged knee joints if the hip joint is not involved and the other knee is serviceable. So often both knees are involved that I must agree with Dr. Kuhns that arthrodesis has not a large field of application.

In the final analysis, prevention is always better than correction and usually easier of accomplishment. The best treatment for a fully contracted knee is to begin treatment early, prevent deformity from occurring and so avoid the necessity of reconstruction surgery.

I want to thank Dr. Kuhns for the thorough manner in which he handled this important subject.

DR. W. P. HOLBROOK, Tucson, Arizona: I could spend the entire time allotted for discussion of this paper in enumerating the points upon which I agree with Dr. Kuhns, so I shall limit my discussion to a few things upon which I do not agree.

First of all, let me raise the point with regard to selecting a suitable time for straightening, manipulation or doing capsuloplasties on flexion contractures of the knee.

I had always been told by my orthopedic colleagues that one should wait until the disease was inactive and until the joint was quiescent. This practice resulted in the accumulation of many stubborn flexion contractures which never became entirely inactive, even after waiting for months and sometimes years.

About 1935 my associate, Dr. Hill, and I decided to see how important this factor was and what would happen if correction of flexion contractures was carried out regardless of disease activity. We selected 19 patients with flexion contractures whose disease was obviously active, for trial. Under deep anesthesia, manipulation was carried out for the purpose of correcting the flexion deformity. These were patients who had failed to correct their deformity with the cast process which Dr. Kuhns described. Four patients required two manipulations to secure correction; four required capsuloplasties, the balance were straightened by simple manipulation on the first attempt. Fourteen of these 19 patients were rechecked a year later and found to be walking with straight legs. Since this time we have done many such manipulations with equally satisfying results.

I wish to emphasize the point that waiting too long for activity of the disease to subside will end in more stubborn contractures and that the sooner a flexed joint is straightened the more satisfactory is the ultimate result.

We fully approve of a period of relaxation in corrective casts, but if the leg does not straighten very promptly within a few weeks or months, more drastic procedure should be carried out without delay.

This brings me to the second point which concerns the value of manipulation in which I seem to be in disagreement. Soft, gentle manipulation will restore many of these flexion contractures to a perfectly straight leg without the necessity of dangerous manipulation or capsuloplasty.

Until manipulation has been attempted under deep anesthesia, it is impossible to tell whether the deformity will be corrected fairly easily or not. Our results with manipulation have been so satisfactory in general that we have done fewer and fewer capsuloplasties.

The third point upon which I wish to disagree is the question of the degree of correction necessary in a flexion contracture. I agree that if you have a 60 or 80 degree knee flexion contracture and will reduce it to 15 degrees, you have placed the leg in a position in which the patient may be able to walk, but if you allow walking on a 15 degree flexion contracture, very shortly that contracture will become 20 or 25 degrees. The flexion contracture will recur and the patient will again become bedridden.

We have felt that even a 5 degree flexion should be watched most carefully before allowing much walking. If possible, we carry our correction of the contracture to

where the leg comes back to complete extension and the entire group of hamstring muscles are relaxed and not taut.

The fourth point is that one must be very careful in allowing walking even with a very small degree of contraction until sufficient time has elapsed for healing and an adequate course of corrective muscle exercises completed. If weight bearing is allowed too soon, before muscle tone is sufficient to maintain weight in the erect position, flexion invariably recurs.

The last point concerns the occasional loss of flexion following a manipulation or operative procedure. Most of these occur because of failure to begin passive and assistive exercises early enough. We have had relatively few in this group and those were in joints so badly destroyed that the manipulative procedure was done without much hope of securing a moveable joint.

I wish to thank Dr. Kuhns for such a timely and scholarly paper.

DR. EDWARD F. HARTUNG, New York City: I would like to ask Dr. Kuhns if one case he showed did not have a posterior dislocation of the tibia. This brings up a very important point. In our experience the main disadvantage of any form of correction except posterior capsulotomy is the great frequency of a sequential subluxation of the tibia. In our experience, unless the correction is attempted within the first year and unless the deformity is very slight, almost any form of correction except an open operation will result in a subluxation. In severe and long standing flexion deformities at the knee the only effective treatment is posterior capsulotomy. An additional observation we have made is the inability of the patient to extend the leg completely even after an open operation, owing to the lengthening of the quadriceps as a result of the prolonged flexion deformity. We commonly meet this situation by transplanting the tibial tuberosity distally.

DR. LORING T. SWAIM, Boston, Massachusetts: I personally feel that many of these corrective things should never have to be performed. Our real job is to get these cases early and treat them adequately by prevention so that we will not have to resort to operative or manipulative procedures to get them corrected. If we could get the cases early enough the possibility of flexure contraction would be taken into consideration in the very beginning and prevented at the start.

DR. JOHN G. KUHNS, Boston, Massachusetts: I am very grateful for the disagreement of opinion. I think you will see that as there was much disagreement among those who treat acute rheumatism, there is just as much disagreement among those who treat flexion contractures.

In regard to the manipulation, we begin just as with any correction and as we did with the changes of casts which I have described.

As to the question of arthrodesis being a useful procedure, in the past few months I have seen four patients who had arthrodeses performed by general surgeons who came into our clinic with arthritis in the other knee and in the back. What was I to do? There was nothing left to do.

I was enthusiastic about manipulation at first. When I first went to the Robert Breck Brigham, Dr. Swaim was very kind to me and permitted me to manipulate a number of flexed knees. Most of those knees are ·stiff in extension and I am not certain whether it would not have been better to leave them as they were with a little motion in flexion.

A mild flexion contracture is not always disabling. I have had several old ladies who would not submit to operative procedures in whom I have attempted corrections. I have been working on those knees for a matter of five years or more and there has been no appreciable change. Probably if I took roentgenograms I would notice some lipping. Probably there would be trouble in the back. That lantern slide to which Dr. Hartung referred did not show a subluxation of the tibia. If you have a flexion deformity of more than 30° it may look like a subluxation.

THE TOCOPHEROLS (VITAMIN E) IN THE TREATMENT OF PRIMARY FIBROSITIS

By CHARLES LEROY STEINBERG, M.D., *Rochester, New York*

THE therapy of primary fibrositis has been most unsatisfactory, and there is no unanimity of opinion regarding it.   Previous communications have called attention to the similarity in the pathologic lesions between so-called nutritional muscular dystrophy and primary fibrositis.   Mackenzie and McCollum have shown that the development of nutritional muscular dystrophy is accompanied by an increase in urinary creatine excretion, and improvement by decrease in urinary creatine.

Creatine excretion studies were done on 15 cases of primary fibrositis by the Folin microchemical method.   After tocopherol therapy these studies were repeated on 13 cases.   The creatine excretion was increased in all cases before therapy was started.   The total amount of creatine varied from 264 to 918 mg.   The creatine was increased above 300 mg. in 12 cases.   Tocopherol therapy had a marked effect in reducing the urinary creatine excretion. In one instance the creatine dropped from 750 to 95 mg. after one week of therapy, in another from 495 to 110 mg., and in another instance the creatine excretion dropped from 706 to 196 mg. after seven weeks of tocopherol therapy.   The daily urinary creatine excretion varied from 86.4 to 140 mg. daily in a control group of ten normal individuals.   Two cases of progressive muscular dystrophy had urinary creatine excretions of 504 mg. and 329 mg. respectively.

One hundred forty-five cases of primary fibrositis have been treated successfully with the tocopherols (vitamin E).   The preparations, dosage and method of administration were as follows: Sixty cases of primary fibrositis were given daily by mouth for the first week 200 mg. of natural mixed tocopherols in oil, which was equivalent to 180 mg. in vitamin E activity expressed as alpha tocopherol.   Half of this dosage was given thereafter.   Ten cases of primary fibrositis were given 200 mg. of alpha tocopherol intramuscularly at weekly intervals along with the oral treatment. Thirty cases of primary fibrositis were given 2 to 8 c.c. of wheat germ oil daily by mouth.   Twenty-one cases of primary fibrositis were given 200 mg. of alpha tocopherol intramuscularly at weekly intervals.   Nine cases of primary fibrositis were given 334 mg. of mixed natural tocopherols intramuscularly at weekly intervals.   This preparation caused severe local reactions in all instances and systemic reactions in three instances.   The local reaction consisted of localized pain, increase in local heat and swelling.   The local lesion healed leaving a firm fibrotic area.   No suppuration occurred. The systemic reaction consisted of increased generalized aches, soreness and slight increase of temperature.   This reaction was later traced to the presence of about 18 per cent of vegetable sterols in the preparation.   These sterols, of course, are entirely unobjectionable orally, but are not readily

assimilated by tissue.   Nine cases of primary fibrositis were given 65 mg. of alpha tocopherol succinate, six cases the same amount of gamma tocopherol palmitate three times daily by mouth.   One hundred forty-three out of the 145 cases treated in this manner were completely relieved of all symptoms in a period of from one to three weeks after starting therapy.   Two cases that received wheat germ oil were only slightly improved.   Four cases were treated by inunction with the natural mixed tocopherols without benefit.

A careful history and physical examination are carried out to establish or refute a diagnosis of primary fibrositis.   A biopsy or urinary creatine determination or both are done on questionable cases.   Three hundred mg. of the natural mixed tocopherols in oil are given daily by mouth during the first week.   Half this dose is given for the next two to three weeks.   Bile salts along with oral tocopherol therapy have been given to a recent group of cases studied.   It is too early to evaluate results from this therapy.   Sixty mg. of natural mixed tocopherols in oil are given daily by mouth for an indefinite period after complete recovery.   This dose is maintained with the idea that the daily requirement of this vitamin is in the neighborhood of 1 mg. per kilo of body weight.   Some of our patients have been observed for a period of 16 months under this management.   No toxic effects have been noted.

Discussion on paper of Dr. Steinberg, "The Tocopherols (Vitamin E) in the Treatment of Primary Fibrositis"

K. HICKMAN, Ph.D., Rochester, N. Y.: I should warn you that I am not a medical doctor but a physical chemist who has become interested in vitamin technology.   My firm prepares fat-soluble vitamins by high-vacuum distillation in the same town in which Dr. Steinberg lives.   Our research laboratory has been experimenting on vitamin E for some years and we have had the privilege of sending various vitamin compounds to Dr. Steinberg who has applied them in his work.

Apparently primary fibrositis is the first human deficiency condition which has been found definitely to respond to vitamin E.   This is in contrast with the doubtful response of human maternity cases to this vitamin.

I shall use the limited time at my disposal to describe certain aspects of the chemistry of vitamin E rather than to discuss Dr. Steinberg's paper directly.   The vitamin was discovered 20 years ago by Evans and co-workers as a material which would cure an artificially induced sterility in rats.   It was at once assumed that the vitamin should play a similar part in human medicine, curing *naturally-occurring* sterility conditions and particularly female abortion.   Similar hopes were entertained for vitamin E in farm animal nutrition.   These hopes have been partially realized in the latter case but have failed to materialize in human medicine.

In spite of these failures, it was evident that vitamin E, which occurs in nearly all foods and especially in fats and in tissues near the seed or reproductive organs, must have some important function.   It was already known that vitamin E is the usual natural preservative of fats which quickly go rancid unless they contain 1–10 parts in 10,000 of the vitamin.   It occurred to us that perhaps the vitamin preserves not only the fat but the body tissues in contact with fat and the oil-soluble vitamins contained in the fat and the tissue.   This belief was strengthened by Moore's observation that the quantity of vitamin A found stored in the liver of the rat is proportional to the amount of vitamin E in the diet.

We have conducted experiments on the synergy of vitamin E with vitamin A and carotene. The method has been to test the increase of rate of growth induced by vitamin A or carotene when differing amounts of vitamin E are given simultaneously. The synergy turns out to be very pronounced, a quantity of carotene which is insufficient to support life in the absence of vitamin E becoming entirely adequate in the presence of the optimum quantity of E. On the other hand, in the complete absence of carotene the vitamin E is unable by itself to support life.

The synergy of these two oil-soluble vitamins is an important but isolated phenomenon. To make out a proper case for vitamin E, other related instances must be found. Dr. Steinberg has shown that vitamin E controls the quantity of creatine degraded from human muscle; experiments which we are sponsoring at the Strong Memorial Hospital in Rochester are showing that the vitamin E minimizes the destruction of vitamin A during juvenile fevers. If the present cures of fibrositis collected by Dr. Steinberg can be repeated with vitamin E elsewhere, it will be evident that the vitamin is playing as important a part in controlling the metabolism of muscle fiber as in controlling the survival of creatine and the fat-soluble vitamins. It suggests that vitamin E should be considered in other rheumatic and neural conditions in which other factors may be wasting in the absence of the vitamin. It is significant that the content of vitamin E in the modern diet is less than half that it is likely to have been in the diet of primitive man.

I have one minor criticism of Dr. Steinberg's paper which is that he has necessarily applied to human medicine a technic which would not be tolerated in the biological laboratory. He has striven for 100 per cent cures and since these have been obtained with doses of different magnitude, we can not tell from his present work what is the minimum curative dose of vitamin E. My belief is that this dose will prove to be smaller than that used by Dr. Steinberg, especially when the dosage is spread over every meal rather than given once daily. This smaller dosage, relatively unimportant clinically, may be significant where the vitamin has to be administered to those in straightened circumstances.

Dr. H. M. Margolis, Pittsburgh, Pennsylvania: Fibrositis, a condition met so frequently in practice, has received altogether too little study. Therefore, any additions to our understanding of this disease and especially any suggestions toward improving its treatment are indeed welcome. Dr. Steinberg's report raises several questions. In view of the biopsy findings and the creatine excretion changes, one gets the impression that the cases under consideration in this report are examples of true muscular fibrositis or muscular rheumatism. For it would be remarkable if vitamin E induced such an effect on the metabolism of tendinous structures, with alteration of the creatine excretion. One wonders, then, whether cases of so-called interstitial, capsular, or periarticular fibrosis have been included in this study.

In my own experience, true muscular fibrositis, with tender, palpable rheumatic nodules has been a rarity. By and large the cases of fibrositis we see are examples of capsular fibrositis, involving tendinous structures, in which we wish vitamin E were effective. It would, therefore, be helpful if Dr. Steinberg could tell us whether he makes such a diagnostic distinction between the various types of fibrositis and what his results have been in these different varieties of the disease.

Dr. M. H. Dawson, New York City: I should like to ask what are the clinical criteria on which a diagnosis of so-called "primary fibrositis" is made? The term is used so loosely that one cannot escape the conclusion that it is applied to a whole group of diseases including "psychosomatic rheumatism," bursitis, postural strain, occupational and traumatic conditions, etc. That such a variety of diseases should respond to one therapeutic agent seems fantastic.

Dr. E. F. Rosenberg, Chicago, Illinois: Dr. Steinberg has shown us photographs of severe Dupuytren's contracture, in illustration of a clinical form of fibrositis. Subsequently he has told us that he has been able to cure fibrositis in a large percentage of his cases with vitamin E. I would like to ask him whether he wishes to imply that severe Dupuytren's contracture can be cured by vitamin E.

Dr. D. M. Angevine, Wilmington, Delaware: I should like to ask three questions: (1) On how many patients were biopsies performed? (2) How many biopsies were done both before and after therapy? (3) Was the creatine tolerance determined on any of these patients?

Dr. Charles LeRoy Steinberg, Rochester, N. Y. (closing): In reply to Dr. Hickman about scaling down the dose, there may be a revision of the dosage. The maintenance dose described by Mackenzie and his coworkers was 0.6 to 1.0 mg. per kilo of rabbit body weight.

Dr. Margolis brought up the question whether these cases were all muscular or periarticular fibrositis. It is difficult to be certain of the diagnosis of periarticular fibrositis in our experience. Later observation often proves these cases to be something other than primary fibrositis. All cases reported in this paper were fibrositis affecting muscle, tendon or aponeurosis.

Dr. Dawson asked by what criteria we make a diagnosis of primary fibrositis. The clinical history is most important. Given a healthy appearing individual whose muscles stiffen ("jell") on the least exposure to cold, who often must lose time from work because of generalized stiffness and soreness, whose blood picture is normal and who shows on careful examination of the skeletal structures, such tell tale evidences as fibrous nodules, thickenings in various planes of aponeuroses and tendon contractures without known cause a presumptive diagnosis of primary fibrositis should be made. If in addition, the urinary creatine excretion is increased and this creatinuria responds favorably to tocopherol therapy, then a positive diagnosis can be made. In other words, a diagnosis by exclusion is most important.

As to the question as to whether we have cured a case of Dupuytren's contracture, my experience is as follows: In no instance of marked contracture have we been able to improve the condition by medical methods. The skin of the palm of the hand is thick and leathery. Tocopherol therapy has returned this tissue to a more normal appearance. I have treated three early cases of Dupuytren's contracture involving one digit on each hand with tocopherol therapy and splinting the digit during the night. These three cases have markedly improved.

In reply to Dr. Angevine's question, 12 cases were biopsied. No follow-up biopsies on the treated cases were done.

CASE REPORTS

A CASE OF MULTIPLE MYELOMA WITH LIVER INFILTRATION AND A LOW PROTHROMBIN PURPURA *

By John A. Schindler, M.S., M.D., F.A.C.P., *Monroe, Wisconsin*

This case of multiple myeloma is being reported because of certain features that are rarely reported in the literature on multiple myeloma.[1] In half the cases of multiple myeloma the soft tissues, particularly the liver, spleen, and kidneys are invaded by the typical round cells closely resembling plasma cells and having little or no intercellular substance.[2] The case presented demonstrates such invasion and a resulting liver damage of such advanced degree as to give rise to most of the symptoms and signs the patient presented, most notably a purpura initiated by a low blood prothrombin.

CASE REPORT

W. K., aged 67, white, had always enjoyed extraordinarily good health, working daily as a carpenter. His family history was not revealing. His habits were good. He stated that he felt well until August 7, 1940, when he slipped and fell on his back while carrying a heavy piece of lumber. He felt an immediate pain in his back which, though not severe enough to disable him, continued as a constant soreness from that time on. It was not until three months later that he had any other soreness, and that began in his right anterior chest about December 1, 1940.

Within a week after his fall, he noticed weakness which began insidiously and gradually increased so that by mid-November, 1940, he had to stop work and by December 1, 1940, he was so weak as to be hardly able to walk.

Some time in August, too, a short time after his fall, he began to lose his zest for eating; he frequently felt nauseated, and he became more and more constipated. Even in October he noted an occasional black, sticky, foul stool. These symptoms increased in severity and by November 15, 1940, he could eat very little without feeling full; and vomiting, which consisted of recently eaten food, occurred almost daily. On November 16, 1940, he had a stool well mixed with bright red blood, and at frequent intervals more blood appeared, never in large amounts. His constipation by that time had become so severe that only large doses of castor oil produced a movement.

Never a heavy man, the loss of 20 pounds from August to December left him a very emaciated figure. He sought the aid of several physicians and clinics; his gastrointestinal tract was examined by roentgen-ray without finding any disease. He was placed by his last doctor on a high vitamin intake and iron for his anemia.

He entered St. Clare Hospital on December 12, 1940.

Physical Examination. The physical examination revealed a man well preserved for his years, quite emaciated, and able to a limited extent to walk around. His temperature was 98.8° F. orally, pulse 80, respiration 18, and blood pressure 130 mm. Hg systolic and 70 mm. diastolic. The positive physical findings were:

(1) In both retinae were numerous scattered small recent hemorrhages. The blood vessels had a normal appearance. (2) There was a marked pallor to his skin and mucous membranes. (3) The gum margin showed oozing hemorrhages. There were petechiae scattered over the oral mucous membrane and over the skin on the thighs. (4) In the axillae and inguinal regions there were a few pea-sized elastic, movable lymph nodes. (5) The left eleventh and twelfth ribs were fairly tender to the touch as was one spot anteriorly on the right fourth rib. (6) There were fine râles scattered through the left posterolateral thorax. (7) The liver presented a smooth, rounded edge and extended three fingers' breadth below the right costal margin. The spleen was not palpable. (8) In the left costo-vertebral angle a hard smooth mass descended on inspiration. This could not be palpated laterally nor anteriorly. (9) Several enlarged, tortuous veins extended from the lower abdomen, over the costal margins and disappeared on the chest. The heart, prostate and neuromuscular systems presented no abnormalities.

The first diagnostic consideration was a differentiation between four widely varying conditions: (1) Hypernephroma with bone metastases, (2) cirrhosis of the liver, (3) carcinoma of the colon with metastases, and (4) leukemia or other blood dyscrasia.

The steps whereby the correct diagnosis was established will not be rehearsed. The first clue was found on the second day when a marked rouleaux formation of red blood cells was noted. With this guide post the establishment of the correct diagnosis was a simple affair.

Laboratory Data. The laboratory data gathered within a few days of his entrance to the hospital were: Red blood cells 1,480,000. Marked anisocytosis. Hemoglobin 3.8 gm. per cent. Hematocrit 12 per cent. White blood cells 5,000. Schilling differential count eosinophiles 1.0; basophiles 0; myelocytes 0; juveniles 0; stab. 13; segmented 33; small lymphocytes 51; large lymphocytes 2; monocytes 2. Bleeding time 14 minutes. Coagulation time 3 minutes. Prothrombin time (method of Quick) 56 seconds. Sedimentation rate 10 mm. per minute. Platelets 280,000. Fragility of red blood cells, beginning hemolysis 0.4 per cent, complete hemolysis 0.32 per cent. Takata-Ara test, positive. Hippuric acid synthesis 1.3 gm.; van den Bergh, slight direct reaction, 0.3 mg. per cent; non-protein nitrogen 44 mg. per cent. Urea 8 mg. per cent. Chlorides 490 mg. per cent. Total blood protein 6.83 gm. per cent. Calcium 6.04 mg. per cent (repeated). Phosphorus 5.0 mg. per cent (repeated). Gastric analysis fractional, free HCl of 49. Total acid of 86. Cevitamic acid 1.7 mg. per cent. Urine: specific gravity 1.012, albumin 3 plus, sugar 0; casts one plus, erythrocytes 3 to 4 plus, no Bence Jones protein. Bone marrow, sternal puncture, no marrow (repeated) but plasma-like cells in considerable number, having an abnormally large nucleus. So thin was the sternal plate that the hypodermic needle easily fell through it while infiltrating with novocaine.

Roentgenological. No defects of the skull were noted except a well circumscribed loss of density in the right mandible. The fourth anterior right rib, and the eleventh and twelfth left ribs showed punched out areas of rarefaction.

No defects of the spine and pelvis could be found.

The barium enema could not be introduced higher than the mid-sigmoid. At this point the barium column ended in a smooth constriction. The examiner classified the constriction as spastic rather than neoplastic.

Though the bones of the upper and lower arms were normal, all the long bones of the hands showed numerous punched out areas of decreased density.

Course. The patient was given 4 mg. daily of 1 methyl 1–4 naphthaquinone intravenously. In spite of this the prothrombin time did not deviate in the slightest. He was given B complex and cevitamic acid and a high carbohydrate intake by mouth. The rectal and urinary bleeding continued and six blood transfusions merely served to

raise his red blood count to 2,000,000. He appeared to be somewhat stronger and felt better, but on January 2, 1941 he suddenly became stuporous, his breathing stertorous, and examination revealed a complete paralysis of the entire right side. He died within a few hours.

Necropsy. The important features at the necropsy were a pathological fracture of the fourth right rib anteriorly. The liver was a pale granular grayish brown. In the colon were numerous hemorrhagic areas the largest of which were in the sigmoid, and here in two of the larger hemorrhages shallow ulcerations were present. Both kidneys were paler than normal with numerous small hemorrhagic areas scattered over the surface. The urinary bladder mucosa was highly hemorrhagic with old adherent blood clots in many places. In the brain were numerous small recent hemorrhages.

In the microscopic section of the liver, the sinusoids were dilated and literally packed with cells characteristic of the plasma cells of multiple myeloma. The liver cells themselves appeared fairly normal. In the kidney the venous capillaries were similarly filled with cells of the plasma type. In the marrow of the fourth rib the erythrogenic and leukogenic centers were entirely obliterated by an overgrowth of myeloid cells becoming plasma-like in numerous areas. In one of the inguinal nodes the sinusoids were filled with similar cells.

COMMENT

The rouleaux formation of the red blood cells which afforded the diagnostic sign post is thought always to occur with a hyperglobinemia. The total protein level here was 6.83 gm. per cent or normal. However, the albumin and globulin fractions were not separately done. In severe liver damage one may expect a marked inversion of the albumin-globulin ratio, not because globulin is increased, but because albumin is decreased. One can only conjecture whether a hyperglobinemia was present or not; certainly not one of very high grade.

The aggregation of red cells in rouleaux formation is doubtless in great part responsible for the extremely rapid sedimentation rate of 10 mm. per minute.

When an increased prothrombin time is not affected by intravenous injection of adequate amounts of synthetic vitamin K, critically severe damage of the liver has occurred. Severe liver damage in my experience is the only explanation of such a phenomenon. The clinical and laboratory evidences of liver damage in this case were enlargement of the liver, development of collateral circulation, a positive Takata-Ara test, a hippuric acid synthesis of 1.3 gm. and the prolonged prothrombin time not amenable to vitamin K therapy. That he died of the results of hemorrhage is definite. His course from the onset of his first symptoms to his death was a matter of only four months. The average duration of the disease was found by Geschickter[3] to be 24 months and by Batts[2] 24 months.

Though the blood calcium is by no means always increased in multiple myeloma, paralleling as it does the blood protein levels, it is distinctly unusual to have so low a figure as 6.04 mg. per cent. The patient had jerking and twitching, a positive Chvostek sign, but never went into tetany. I have seen similar low calcium figures in cirrhosis of the liver in which case it was usually accompanied by osteoporosis.

The high blood phosphorus is not unusual in multiple myeloma.

The question must necessarily arise whether such a case as this should be called a plasma-cell leukemia, the only criterion of which is the constant finding

of plasma cells in the blood,[4] or a diffuse plasma-cell myeloma. In this case no plasma cells were found in the circulating blood; it is possible the examination was insufficiently thorough. Until more is known of the origin of this type of cell, the classification is uncertain.

Clinically, this case is interesting since the patient showed four of the six cardinal symptoms and signs of multiple myeloma listed by Geschickter and Copeland [5]:

1. Multiple skeletal tumors in a person over the age of 35,
2. Spontaneous fractures, usually a rib,
3. Bence-Jones bodies in the urine,
4. Lumbar pain with early paraplegia,
5. Unexplained anemia.
6. Chronic nephritis with azotemia and low pressure, and yet these were overshadowed by the manifestations of purpura, the bleeding gums, hemorrhagic retinae, melena, hematuria, and skin and mucosal petechiae. Next to purpura in clinical importance was the apparent obstruction of the sigmoid, which was found to be due to spasm at the site of the ulcerations into the hemorrhagic necrosis, and finally there was the clinical appearance of hepatic cirrhosis.

In regard to the liver, the cells of which appeared fairly normal, but the sinusoids of which are so densely packed by myeloma cells, it is interesting to note what measurable functions were and were not impaired. The excretory function, as judged by the absence of jaundice and a van den Bergh of 0.3 mg. per cent was unimpaired. The most marked impairment was the inability to utilize vitamin K in the formation of prothrombin, etc. The formation of urea (8 mg. per cent) was likewise impaired.

SUMMARY

1. A case of multiple myeloma is presented in which a striking invasion of the liver sinusoids by plasma-cells had occurred.
2. The most prominent clinical aspect of the patient was a marked purpura.
3. The purpura was due to a low blood prothrombin which was unaffected by large intravenous doses of 2 methyl 1–4 naphtholquinone.
4. Other clinical and laboratory evidences of severe liver damage were found.

BIBLIOGRAPHY

1. MALLORY, T. B.: Case records of the Massachusetts General Hospital, Case No. 22502, New England Jr. Med., 1936, ccxv, 1132.
2. BATTS, M.: Multiple myeloma. Review of forty cases, Arch. Surg., 1939, xxxix, 807–823.
3. GESCHICKTER, C. F., and COPELAND, M. M.: Tumors of the bone, Revised Ed., New York. Am. Jr. Cancer, 1936.
4. PATEK, A. J., and CASTLE, W. C.: Am. Jr. Med. Sci., 1936, cxci, 788.
5. GESCHICKTER, C. F., and COPELAND, M. M.: Am. Jr. Cancer, 1936.

BALL THROMBUS IN THE HEART *

By David M. Spain, M.D., *New York, N. Y.*

BALL thrombus in the heart is a frequently mentioned complication in the course of mitral stenosis. However, reviews of the literature by Abramson (1914) [1] and Aronstein and Neuman (1939) [2] revealed reports of only 31 authentic cases. Recently, Garvin (1941) [3] reported three additional cases. Ball thrombus of the heart is rare, and in only a few cases has the correct ante-mortem diagnosis been made or even considered.

In the laboratories of pathology at Bellevue Hospital during the past year, I have encountered a ball thrombus in which the correct clinical diagnosis was made.

CASE REPORT

The patient, (V. K.), a 33 year old white female housewife, was admitted on August 4, 1940 to the Fourth Medical Division of Bellevue Hospital (Dr. Charles Nammack, Director), following an episode of nocturnal dyspnea and cough with the production of pink frothy sputum. Ten days prior to admission the patient was hospitalized at another institution for cough and increased fatigability. After a few days of bed rest and sedation she was discharged as improved.

At the age of 15 she complained of "growing pains" but never had chorea or polyarthritis. Two years prior to admission she first noticed exertional dyspnea, orthopnea and cough. Since that time she had been on digitalis therapy.

Physical examination on admission revealed a thin, pale, young female with marked dyspnea and moderate cyanosis. Moderate dullness and fine to medium moist râles were present over the bases of both lungs, posteriorly. Examination of the heart showed a diffuse precordial heave, an apical systolic thrill and diastolic shock. The point of maximum impulse was in the sixth intercostal space, 3 cm. to the left of the midclavicular line. Regular sinus rhythm was observed and the sounds were of good quality. A localized harsh rumbling presystolic and a diffuse soft blowing systolic murmur were heard at the apex. The pulmonic second sound was louder than the aortic. The liver edge was felt 5 cm. below the costal margin.

While in the hospital the temperature varied between 99°–101° F. for the first three weeks and between 100°–103.5° F. during the last two weeks. Respirations averaged 26 per minute and pulse rate 95.

The sedimentation rate on August 21, 1940 was 41 mm. per hour and on September 4, 1940 was 48 mm. per hour. Several blood counts revealed an average result of white blood cells 13,000 with 78 per cent polymorphonuclear neutrophiles and 22 per cent lymphocytes, red blood cells 3.5 million with 68 per cent hemoglobin (Sahli). Urinalysis showed 1 plus albumin with occasional red blood cells and white blood cells. Five blood cultures were negative. Blood Wassermann reaction was negative and the blood chemistry showed nothing significant. Several electrocardiograms during the five weeks showed sinus rhythm, increased P-R interval, notched P-waves, inverted T_3 and diphasic P_3. Chest plate on August 20, 1940 showed marked interstitial fibrosis at the base of the right lung with thickening of the pleura in the costodiaphragmatic angle. The heart was enlarged in all diameters with fairly marked accentuation of the mitral curve. Chest plate on September 4, 1940 showed consolidation of the right middle and lower lobes.

On August 7, 1940 there was a sudden onset of coldness and numbness of the right hand, the pulse was not palpable and deep cyanosis was present. Cardiac rhythm at this time was regular. Small petechiae were observed in the right conjunctiva. On August 8, 1940 no dorsalis pedis pulsation was evident and there was marked pallor over the dorsum of the right foot and left big toe. This episode was transient. On the evening of August 11, 1940 the patient suffered a coughing spell which was productive of a large quantity of bloody sputum. All the limbs at this time were warm and the pulses were felt except in the right foot where no dorsalis pedis pulsation was present.

On August 14, 1940 faint pulsation of the dorsalis pedis was noted. The chest showed diminished breath sounds at the right base. On August 18, 1940 all pulses were palpable. On several occasions there were transient episodes during which the patient
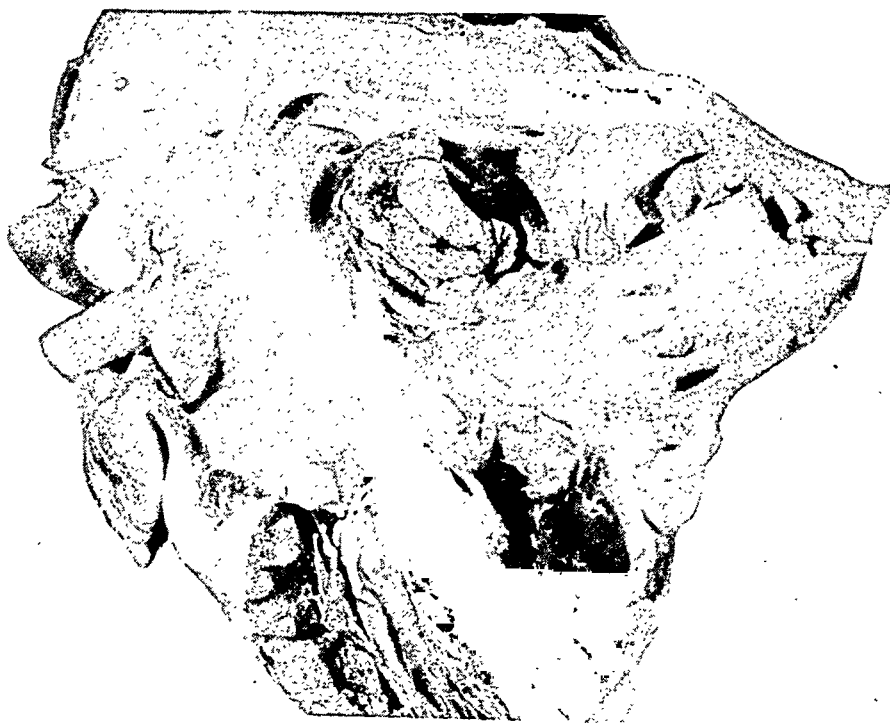
Fig. 1. Ball thrombus in left auricle.

complained of coldness of all four extremities and a slight faint feeling. No blood pressures were taken during these episodes because of their fleeting nature. On August 22, 1940 the patient suffered severe pain in the right flank and numerous red blood cells were detected for the first time in the urine. On August 30, 1940 the temperature rose to 103° F. the patient was coughing up bloody sputum and from this point on she became weaker and died on September 13, 1940.

The clinical diagnosis was rheumatic heart disease with mitral stenosis and insufficiency, pulmonary infarction, multiple embolic phenomena and ball thrombus of the left auricle.

Necropsy Findings. Necropsy was performed 15 hours after death. The peritoneal cavity contained a few hundred c.c. of clear straw-colored fluid. The liver extended 8 cm. below the costal margin. Seven hundred c.c. and 1,000 c.c. of clear straw-colored fluid were present in the right and left pleural cavities, respectively. Infarcts were present in the right lower lobe of the lung and both kidneys. The lungs showed congestion, edema and patchy bronchopneumonia.

The heart weighed 390 gm. The pericardial surfaces were smooth and glistening. On section the right auricle and ventricle were found to be considerably distended by postmortem clot. The right auricle was dilated and the right ventricle was both dilated and hypertrophied. The tricuspid valve appeared to be insufficient and was thickened and shortened. The pulmonary valve was normal. The left auricle was markedly dilated and its endocardium was thickened and roughened. Within this chamber was a roughly spherical, fairly smooth-surfaced, grayish-red mass, measuring 3 cm. in diameter. On section this thrombus consisted of partially organized, lamellated blood clot with a soft, red and necrotic center. It was attached to the posterior lateral surface of the auricle by a long, thin, friable pedicle. The thrombus lay loosely above the mitral orifice (figure 1). The mitral orifice was markedly stenosed as a result of thickening of the leaflets and shortening and fusion of the chordae tendineae. The orifice was likewise insufficient. The aortic valve appeared to be normal. The coronary ostia were widely patent and the vessels appeared to be normal throughout.

COMMENT AND SUMMARY

The left auricular endocarditis, in all probability, was the focus of origin for the thrombus, while the tight mitral stenosis was an important factor in its enlargement into a ball thrombus. The transient episodes of interference with the peripheral circulation were probably caused by intermittent partial obstruction of the mitral orifice by the ball thrombus. These episodes led to the consideration of ball thrombus as the causative factor.

BIBLIOGRAPHY

1. ABRAMSON, J. L.: Ball thrombi of the heart, Ann. Clin. Med., 1924, iii, 327.
2. ARONSTEIN, C. G., and NEUMAN, L.: Ball thrombus of the heart: report of a case with review of the literature, Arch. Path., 1939, xxvii, 907.
3. GARVIN, C. F.: Ball thrombi in the heart, Am. Heart Jr., 1941, xxi, 371.

ENDOCARDITIS DUE TO *PSEUDOMONAS AERUGINOSA* *

By VICENTE MORAGUES, M.D., and W. A. D. ANDERSON, M.D., F.A.C.P., *St. Louis, Missouri*

Pseudomonas aeruginosa (B. pyocyaneus) is a common saprophyte of the skin and gastrointestinal tract.[1] That it may also inhabit the urinary tract is suggested by its occasional isolation from the blood stream following urological operations.[2,3] Being potentially pathogenic, it may invade from any of its usual locations, and cause serious localized or widespread infection. In rare instances localization on a heart valve has resulted in rapidly fatal acute endocarditis. Review of the literature shows only two such cases reported in this country[4,5] and four in German medical literature.[6,7,8,9]

CASE REPORT

D. K., a diabetic white man, aged 66 years, entered the hospital because of general malaise, dyspnea, chills, and burning on urination. For three months he had noticed

progression in the severity of his nocturia, with burning and dribbling at the time of urination. Dyspnea had been present for two weeks. For four days the dyspnea had been severe, and accompanied by high fever, chills, headache and diarrhea.

He was a well developed man, without emaciation, and was rational and co-operative in spite of considerable dyspnea. The respiratory rate was 54 per minute, temperature 106° F., and pulse rate 104 per minute. His systolic blood pressure was 170 mm. of mercury, and diastolic 72 mm. The heart appeared slightly enlarged, though without thrills or murmurs. The rhythm was undisturbed except for occasional extrasystoles. Numerous râles were heard over both lungs posteriorly, and were coarser over the right base where the breath sounds were diminished and vocal fremitus increased. Some dullness on percussion was present posteriorly over the lower lobes.

By catheterization, 1,500 c.c. of urine were withdrawn from a distended and painful bladder, and a retention catheter left in place.

The laboratory findings at this time were as follows: *Urine:* acid; specific gravity 1.023; albumin 2 +; sugar 2 +; red blood count 3,810,000 per cu. mm.; hemoglobin 12 g.; white blood count 16,200 per cu. mm.; segmented forms 80 per cent; stabs 12 per cent; and lymphocytes 8 per cent; Kahn test negative; non-protein nitrogen 46 mg. per 100 c.c.; blood sugar, 238 mg. per 100 c.c.
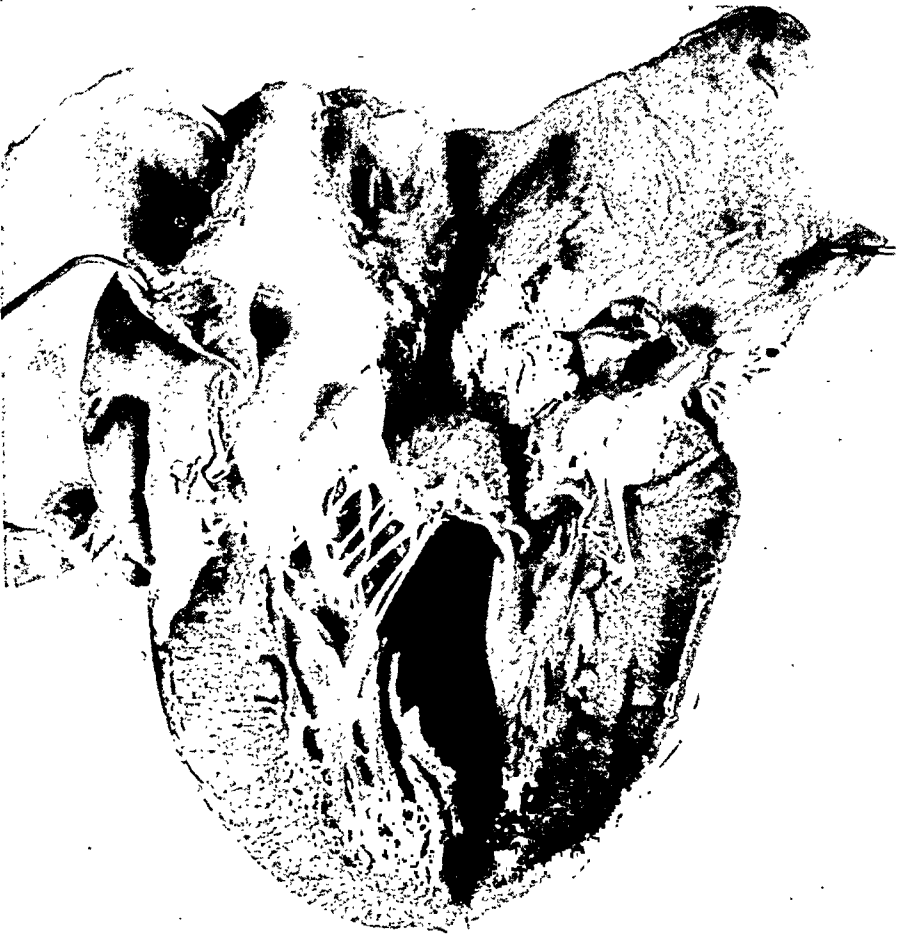
FIG. 1. The heart, showing large vegetations on the mitral valve and some thickening of the chordae tendineae.

On the third day the patient was markedly dyspneic and delirious. The pulse was irregular and rapid. Bronchial breathing could be heard on both sides of the chest. Blood culture on the fourth and sixth days showed *P. aeruginosa*. On the seventh day the chest signs and general condition appeared improved.

The temperature rose again abruptly on the ninth day. The patient became dull and uncoöperative, and had involuntary bowel movements. Neck rigidity was noted, and the Kernig, Brudzinski, and Babinski tests were positive. Spinal fluid pressure was 45 mm. and on jugular pressure rose to 140 mm. The fluid was opalescent and had a cell count of 567 per cu. mm. Tests for globulin were negative, and no growth was obtained on culture.

The patient's condition steadily deteriorated. Blood culture taken on the fourteenth day again showed *P. aeruginosa*. Death occurred on the fifteenth day in hospital.

Autopsy Examination. The main findings at autopsy involved heart, lungs, meninges, and prostate. The heart weighed 300 grams. The mitral valve was thickened and retracted, with some areas of calcification and, apparently, a moderate degree of stenosis. The chordae tendineae were shortened, thickened, and firm. On the auricular surface of the valve were large, extremely friable, grayish vegetations (figure 1). There were areas of ulceration, but no actual perforation of the valve. Some of the vegetations extended onto the endocardium of the left auricle. The left auricle was considerably dilated. The cardiac valves, other than the mitral, were uninvolved.

Smears and sections from the mitral vegetations showed abundant, small, rod-shaped bacteria (figures 2 and 3), identified culturally as *P. aeruginosa*. Sections of the vegetations also showed large masses of necrotic debris and abundant fibrin. The myocardium was edematous and congested. In focal areas there were a few poly-morphonuclear leukocytes between muscle fibers. In some areas coronary vessels were involved by inflammatory changes. The intima showed proliferative thickening, with some chronic inflammatory cells scattered through this portion of the arterial wall.

The lungs showed surprisingly little gross change. A hemorrhagic, infarct-like area about 1 cm. in diameter involved the lower part of the right upper lobe. The only other gross changes were subpleural, calcified, primary tuberculous lesions, and moderate anthracosis and emphysema. In sections, thrombi were evident in small arteries, and about the periphery of the area of necrosis there was fibrinous material and organization. Some alveoli about this region contained polymorphonuclear leukocytes.

Cerebrospinal fluid in the subarachnoid space appeared slightly increased in amount and cloudy. Between some of the convolutions in the region of the vertex it seemed almost purulent. Smears from this region showed many inflammatory cells, and a few small rod-like organisms similar to those from the cardiac vegetations. Cultures from the meninges showed *P. aeruginosa*. Microscopically, the cells in the meningeal exudate were predominantly polymorphonuclear leukocytes. The meningeal blood vessels were prominently involved, both veins and arteries being infiltrated by acute inflammatory cells (figure 4).

The urinary bladder had a thick edematous mucosa with some areas of hemor-rhage. The prostate was considerably enlarged by adenomatous hyperplasia with areas of necrosis and abscess formation in which polymorphonuclear leukocytes were numerous and bacteria could be demonstrated (figure 5). Thrombi involved some of the periprostatic veins.

Small areas of focal necrosis were also present in the spleen. Areas of infarction and acute focal glomerular nephritis were evident in the kidneys. The gall-bladder wall was thickened, with chronic inflammatory cells in submucosa and muscularis.
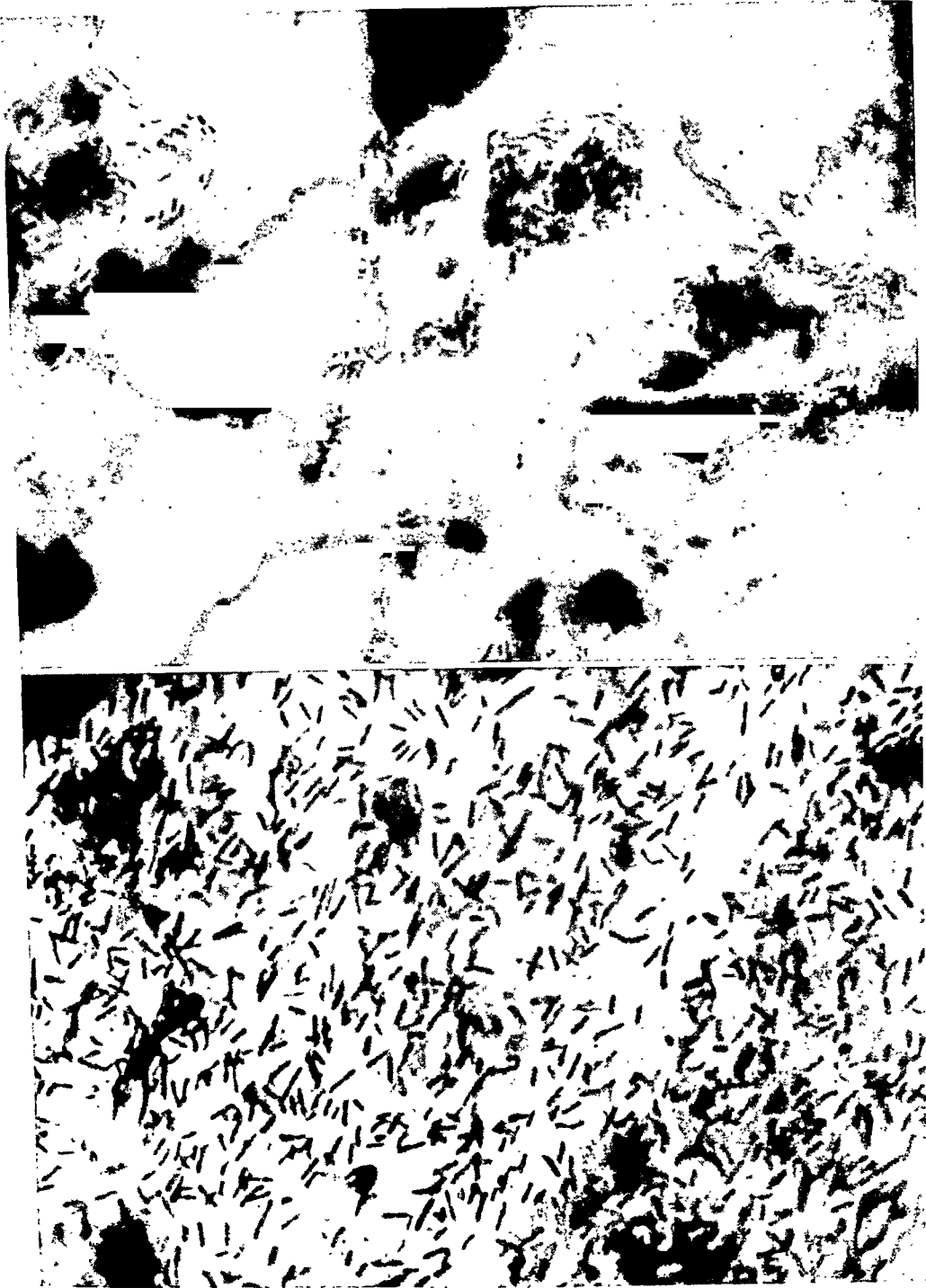
FIG. 2 (above). Microscopic appearance of the vegetations showing many large rods (Giemsa stain).
FIG. 3 (below). Smear from the vegetations showing the same large rods (Giemsa stain).

FIG. 4. Meningeal artery, showing infiltration of the walls with acute inflammatory cells (hematoxylin and eosin).

FIG. 5. Prostate, showing an area of suppuration forming an abscess (hematoxylin and eosin).

The final anatomical diagnoses were: acute bacterial mitral endocarditis due to *Pseudomonas aeruginosa;* old mitral endocarditis with calcification and stenosis; acute myocarditis; acute purulent meningitis; acute meningeal arteritis; infarcts of spleen, kidneys and lungs; acute focal glomerulonephritis; adenomatous hyperplasia of prostate; abscesses of prostate; thrombosis of periprostatic veins; chronic cystitis; acute splenitis; parenchymatous degeneration of liver and kidneys; chronic cholecystitis; hemangioma of liver; obsolete tuberculosis of lungs; mild generalized arteriosclerosis; fatty infiltration of pancreas (diabetes mellitus clinically); pyorrhea and dental caries.

Review of Previously Reported Cases: The six cases of endocarditis due to *P. aeruginosa* which have been previously reported are briefly noted here for the purpose of comparison. Details of these and the present case are given in the accompanying table. The literature was reviewed by Fish, Hand and Keim [5] in 1937. We have been unable to find any case reported since that time.

TABLE I

Tabulation of Cases of *P. aeruginosa* Endocarditis

Author	Blum[6]	De la Camp[7]	Rolly[8]	Thayer[4]	Bungeler[9]	Fish, Hand and Keim[5]	Moragues and Anderson
Age	2½ months	51	28	42	65	71	66
Sex	M	F	F	F	M	M	M
Valve involved	mitral	mitral	mitral	mitral	mitral	aortic	mitral
Previous damage to valve	?	?	yes	?	yes	?	yes
Probable portal of entry	?	skin?	gastro-intestinal tract	gastro-intestinal tract	contaminated intravenous injection	genito-urinary tract	genito-urinary tract
Other tissues involved	?	skin intestines spleen	meninges spleen kidneys arteries	peritoneum; intestines; ovaries	spleen	aorta kidneys	meninges, arteries, spleen, lungs, kidneys, prostate

Blum [6] in 1899 reported the case of a baby boy, two and a half months of age, with typical signs of congenital syphilis. At necropsy, a mitral endocarditis was found, with large numbers of Gram negative bacilli in the vegetations. These organisms were proved to be *P. aeruginosa.*

In 1903, a case of chronic pyocyaneus septicemia with polyarthritis and a hemorrhagic diathesis was recorded by De la Camp [7] in a woman, 51 years of age, who had also blisters, pustules and abscesses on the skin. The autopsy demonstrated bacterial endocarditis of the mitral valve. *P. aeruginosa* were isolated in pure culture from the vegetations.

In 1906, Rolly [8] published the case of a woman, 28 years of age, who had a typhoid-like septicemia two months before admission, during a small epidemic

in the house where she lived.   She also had some meningeal symptoms.   Cultures from blood and spinal fluid showed pure *P. aeruginosa*.   At autopsy there was a bacterial endocarditis implanted on an old rheumatic mitral valve, meningitis and metastatic abscesses of spleen and kidneys.   *P. aeruginosa* was demonstrated in sections of the valve and in the walls of the arteries.

Thayer,[4] in 1926, analyzed the case of a female, 42 years of age, admitted to the hospital with the complaints of diarrhea, vomiting, anorexia, and progressive asthenia, of about three to four weeks' duration.   The temperature was subnormal, the pulse 100 per minute.   The right leg was swollen and edematous, the superficial veins prominent, and palpable thrombi were evident in the saphenous vein.   The diarrhea continued and the patient died seven days after admission.   The autopsy revealed chronic pelvic cellulitis and peritonitis, an ovarian abscess and a recto-vaginal fistula.   There were many ulcerations in small and large intestine with perforation and acute peritonitis; and in addition there was a gastric carcinoma.   The heart showed bacterial endocarditis of the mitral valve.   Cultures from the mitral vegetations, peritoneum, intestinal ulcers and ovarian abscess yielded pure growth of *P. aeruginosa*.   This case occurred in the midst of a rather remarkable epidemic of Pyocyaneus disease with intestinal manifestations.

Bungeler,[9] in 1927, reported the case of a man, 65 years of age, who seven years before death had developed cardiac disease following erysipelas, and who showed physical signs of mitral insufficiency.   Because of a "nervous disease" he was given repeated intravenous injections of a preparation of saprophytic bacteria called "saprovitan."   This preparation was later proved to contain *P. aeruginosa*.   He developed a septicemia and died after 16 days.   The autopsy revealed bacterial endocarditis of the mitral valve with a perforation 1 cm. in diameter in one of the cusps.   No histological or bacteriological study was made of the vegetations.   Cultures from spleen yielded *B. proteus*, *P. aeruginosa* and Gram positive cocci in chains.

The case reported by Fish, Hand and Keim,[5] in 1937, was that of a male, aged 71, who entered the hospital because of inability to void for three days.   He had been catheterized three times during the three days prior to admission.   His urinary symptoms started 18 months previously when he developed acute retention.   This recurred about every six months necessitating catheterization each time.   Other symptoms were nocturia, slow stream and occasional dysuria.   Examination disclosed a symmetrically enlarged prostate.   There was trabeculation of the bladder with several diverticula.   Fourteen days after admission a suprapubic prostatectomy was performed.   On the seventh postoperative day his temperature suddenly rose to 103.4° F.   Six blood cultures before death were all positive for *P. aeruginosa*.   The patient died on the twenty-seventh postoperative day.

Bacterial endocarditis of the aortic valve with large numbers of Gram negative bacilli in the vegetations was found at autopsy.   In the wall of the aorta there were inflammatory cells and Gram negative bacilli.   The kidneys presented several infarcts and the prostate showed hyperplasia and several areas of acute inflammatory reaction though no bacteria should be demonstrated.

COMMENT

Consideration of the case reported here and of those already in medical literature discloses several points of interest. The portal of entry in the present case, as in that of Fish, Hand and Keim,[5] appears to have been the genitourinary tract, probably from a focus in the prostate. Hyman and Edelman [2] and Scott [3] have shown that *P. aeruginosa* may be isolated occasionally from the blood following urological operations. As in other types of bacterial endocarditis, there is a predilection for localization on a valve which is already damaged. Except in one case,[5] the mitral valve was the one involved. From the infected valve, spread may occur to spleen, kidneys, and meninges. Meningitis was a prominent manifestation in the present case as well as in that of Rolly.[8]

An interesting feature of infection with *P. aeruginosa* is involvement of blood vessels, particularly arteries. This vascular inflammation is well demonstrated in the case reported here (figure 4), and was observed also in the cases of Rolly [8] and of Fish, Hand and Keim.[5] This tendency of *P. aeruginosa* to cause vascular inflammation has been studied by Fraenkel.[1] The development of acute focal glomerular nephritis in association with this type of bacterial endocarditis does not appear to have been noted previously.

SUMMARY

1. A case of bacterial endocarditis due to *Pseudomonas aeruginosa*, with meningitis, widespread infection of other organs and focal glomerular nephritis is presented.

2. The six other cases which have been reported are briefly summarized.

3. The importance of the genitourinary and gastrointestinal tracts as a portal of entry for *Pseudomonas aeruginosa* is pointed out. The tendency of this organism to cause acute vascular inflammation is noted.

BIBLIOGRAPHY

1. Fraenkel, E.: Ein weiterer Beitrag zur Menschenpathogenität des Bacillus Pyocyaneus, 1922, xcv, 125–134.
2. Hyman, A., and Edelman, L.: Medical and surgical aspects of hematogenous infections in urology, Jr. Urology, 1932, xxviii, 173–198.
3. Scott, W. W.: Blood stream infections in urology, Jr. Urology, 1929, xxi, 527–566.
4. Thayer, W. S.: Studies on bacterial (infective) endocarditis, Johns Hopkins Hosp. Reports, 1926, xxii, 73–74.
5. Fish, G. W., Hand, M. M., and Keim, W. F.: Acute bacterial endocarditis due to *Pseudomonas aeruginosa* (*B. pyocyaneus*), Am. Jr. Path., 1937, xiii, 121–128.
6. Blum, S.: Ein Fall von Pyocyaneus-Septikämie mit komplizierender Pyocyaneus-Endocarditis im Kindesalter, Centralbl. f. Bakt., 1899, xxv, 113–116.
7. De la Camp: Zur Kenntnis der Pyocyaneussepsis, Charite Ann., 1903, xxviii, 92–111.
8. Rolly: Pyocyaneussepsis bei Erwachsenen, München. med. Wchnschr., 1906, liii, 1399–1404.
9. Bungeler, W.: Über Endocarditis maligna durch *Bacillus pyocyaneus*, Frankfurt. Ztschr. f. Path., 1927, xxxv, 428–435.

GONOCOCCAL MYCOTIC ANEURYSM OF THE AORTA: REPORT OF A CASE SUPERIMPOSED UPON A SYPHILITIC AORTA *

By JAMES H. CURRENS, M.D., and JAMES M. FAULKNER, M.D., F.A.C.P.,
Boston, Massachusetts

MYCOTIC aneurysms involving the aorta and smaller arteries have been reported not infrequently in the literature. Various organisms have been isolated from the site of the aneurysm including the hemolytic and non-hemolytic streptococcus, staphylococcus, pneumococcus, *H. influenzae* and gonococcus. As a rule there is an associated endocarditis of the aortic or, less commonly, of the mitral valve, and it is supposed that the intima of the aorta becomes infected by secondary implantation from the valvular vegetations. A survey of the literature reveals nine cases of mycotic aneurysms resulting from gonococcal infection, which are summarized in table 1. We are reporting this case as the tenth such case. It is apparently unique, however, in that it is the only report known to us of a gonococcal mycotic aneurysm superimposed upon syphilitic aortitis.

CASE REPORT

T. F., a 41 year old Irish-American painter, entered the second medical service on January 27, 1939, complaining of joint and muscle pains of four weeks' duration. Twenty-five years previously he had been infected with syphilis and gonorrhea and over a period of several years had undergone irregular antisyphilitic treatment but received no specific treatment for gonorrhea. Seven years before, in 1932, he had been treated at the Boston City Hospital following a "shock" associated with unconsciousness for several hours and left hemiparesis. At that time he had no cardiac symptoms but there were well marked systolic and diastolic murmurs in the aortic area. The heart and great vessels were not enlarged by roentgenogram. The Kahn test for syphilis was positive in the blood and spinal fluid. Diagnoses of tertiary syphilis, syphilitic aortic regurgitation, and cerebral thrombosis were made. He was treated with intramuscular bismuth for about eight months until he stopped attending the clinic. At that time the Kahn test in the blood was still positive but the paralysis had entirely cleared.

Three years later he spent two days in the hospital following a prolonged alcoholic bout. At that time there was no change in the cardiac murmurs. There was no cardiac enlargement by roentgenogram, and the Kahn test for syphilis was negative in the blood and spinal fluid. An electrocardiogram was likewise normal.

During the succeeding four years he was free of symptoms and remained fairly steadily employed as a painter in spite of continued heavy drinking and an inadequate diet. In December, 1938, he began to have nocturnal attacks of suffocation and substernal pain associated with dyspnea and sweating. The pain often radiated down the inside of the right arm to the finger tips. After about a month of almost nightly attacks they began to diminish in frequency and severity but at the same time he began to have pain, redness, heat and swelling in the right foot and ankle associated with chills and sweats. Later the painful swelling extended to the muscles of the right hand. There had been no previous history of rheumatic fever or chorea.

On admission to the hospital the oral temperature was 104° F., pulse 120 and respirations 26 per minute. He was fairly well developed and nourished and in no acute distress. Dental caries was marked. The heart was not enlarged to percussion and the systolic and early diastolic murmurs previously noted were present in undiminished intensity. The radial pulses were equal. The blood pressure was 150 mm. Hg systolic, 70 mm. diastolic. A smooth tender liver edge was felt three fingers' breadth below the costal margin. The spleen was not felt. There were redness and swelling about the metacarpo-phalangeal joints of the right hand. There were also tenderness and pain on motion of the right shoulder joint. The prostate was enlarged, boggy and tender. There were venereal warts on the glans penis. The deep tendon reflexes
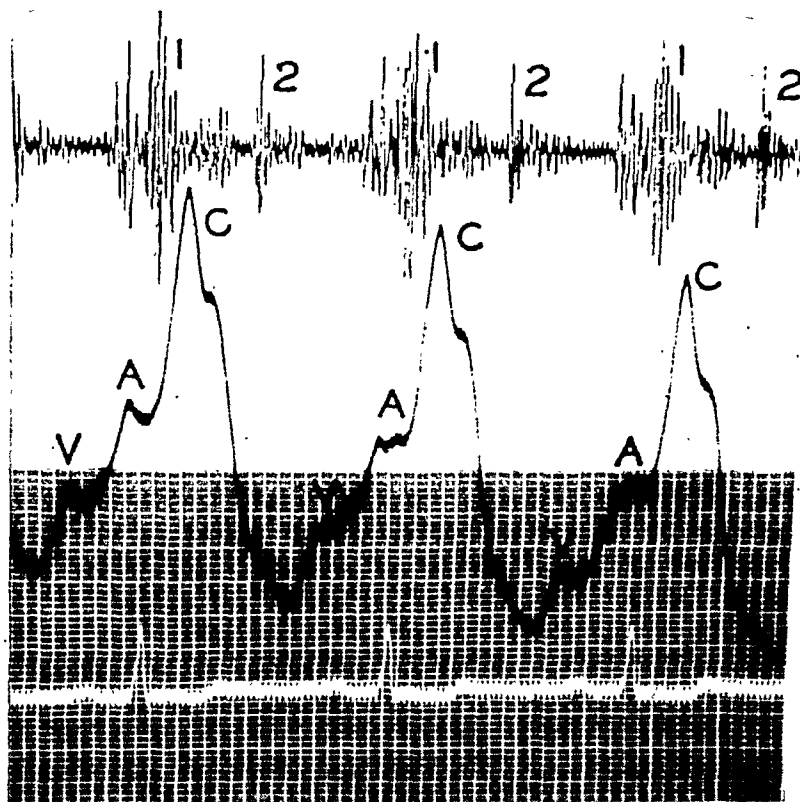
FIG. 1. Phono-electrocardiographic tracing taken just medial to the apex three weeks before death. The murmur preceding the first heart sound is the presystolic murmur and begins just prior to the peak of the A-wave. (We are indebted to Dr. E. A. Stead and Dr. Paul Kunkel for the use of this tracing.)

were hyperactive on the left. Laboratory findings were as follows: Blood hemoglobin 11.7 gm.; erythrocyte count 4,600,000: leukocyte count 19,000; with a differential of 72 per cent polymorphonuclear leukocytes, 7 per cent band forms, 15 per cent lymphocytes, 2 per cent monocytes, 3 per cent eosinophiles, and 1 per cent basophiles. Red blood cells and platelets were normal. Examination of the urine was negative except for 3–5 leukocytes, 2–3 epithelial cells, and an occasional red blood cell per high power field. There were no casts. Stool examination was negative for occult blood. The Hinton test for syphilis was positive in the blood as was a gonococcus complement fixation test. The non-protein nitrogen in the blood was 30 mg. per 100 c.c. and the total protein 6.5 grams. Agglutination tests for the enteric group of organisms and a prostatic smear and culture were negative. A roentgenogram of the chest and a retrograde pyelogram were likewise negative. An electrocardiogram was normal.

Course. During a period of 18 weeks in the hospital the patient had an irregular fever of 100° to 102° F. Because of a strong but unconfirmed suspicion that the infection was gonococcal in origin he was given three courses of sulfanilamide (6 grams per day). In each instance there was a temporary decline in fever with improvement which was not maintained in spite of continued treatment. Because of progressive secondary anemia, aggravated by the sulfanilamide, he was given three transfusions of 500 c.c. of whole blood. Eighteen blood cultures planted both aerobically and anaerobically were negative. The nineteenth and twentieth cultures, both taken five days before death, were reported positive for gonococcus after the patient had died.

The patient continued fairly comfortable, ambulatory, part time, for four months when he suddenly developed an attack of acute pulmonary edema apparently precipitated by a vomiting attack. This was the first sign of cardiac failure. At this time a distinct mitral diastolic crescendo murmur became audible at the apex (figure 1). Paroxysmal dyspnea and orthopnea became increasingly severe; edema of the extremities appeared, and there were severe nose bleeds and bloody stools. There were no petechiae. Three days before death the spleen became palpable. After 24 hours of progressive pulmonary edema, the patient died.

NECROPSY FINDINGS

Anatomical Diagnosis. Syphilitic aortitis with superimposed mycotic aneurysm (gonococcal). Lobar pneumonia, left lower lobe, type 17, with pleuritis. Syphilitic aortic valvulitis with aortic insufficiency. Septic infarcts of the spleen. Acute focal embolic glomerulo-nephritis.

The heart weighed 450 grams with enlargement primarily of the left ventricle. The tricuspid, pulmonary and mitral valves were normal. The commissure between the anterior and left posterior cusps of the aortic valves was widened so that there was a groove between the two cusps measuring about 0.6 cm. in width. The cusps were partly calcified in the region of this lesion so that it formed a rigid aperture which prevented the valve from closing completely. The leaflets and other commissures were normal. The endocardium of the left ventricle showed several fibrous plaques in the region of the aortic valve, these plaques being distributed in an oblique line across the endocardium beginning at the separation of the commissures mentioned above and ending at the lateral border of the left ventricle, seemingly marking the direction of the regurgitation of blood which probably occurred during life. The endocardium was otherwise normal. The aortic intima was covered with scattered lesions of two varieties, one consisting of irregular, raised, yellow plaques averaging 5 mm. in diameter and the other characterized by oval to round lesions cream-colored to white. For a distance of 9 cm. above the aortic valve the aorta was dilated having a circumference of 7.5 cm. while the more distal aorta, in which the raised plaques already described were more prominent, measured 5.0 cm. in circumference. Five centimeters above the aortic valve in the dilated portion of the aorta a spherical mass of grayish-red friable tissue was attached to the intima. When the mass was removed, a saccular aneurysm was revealed, the opening of which measured 1.5 cm. in diameter (figures 2 and 3). Friable grayish-yellow material was attached firmly to its margins and the sac measured 4 by 2 cm. It was filled with an old blood clot and impinged upon the left auricle. The left lung weighed 1340 gm. and the left lower lobe was consolidated and bluish-gray on cut surface.

The spleen weighed 380 gm. and was dark reddish-purple in color with an infarct measuring 5 cm. by 3 cm. extending to the surface and exuding yellow purulent material on cut surface.

The liver weighed 2,060 gm. The slightly enlarged kidneys had a combined weight of 380 gm. The capsular surface was smooth with a moderate number of

petechial hemorrhages over the surfaces of both kidneys and several dull red raised areas, the largest measuring 2½ by 2 cm. The prostate was of usual size and consistency without abscess or evidence of infection. The seminal vesicles and testes were negative.

Microscopic Examination. The heart muscle was normal. The alveoli of the left lower lobe of the lung were filled with polymorphonuclear leukocytes and fibrin.

FIG. 2.   Photograph of the heart and aorta. A. Mycotic aneurysm. B. Deformed aortic valve with separation of the commissure. C. Roughened fibrous plaque.

There were multiple areas of focal necrosis with polymorphonuclear leukocytes throughout the spleen. The epithelium of the rectum was absent over a wide area. The glomeruli of the kidneys showed focal necrosis, infiltration with polymorphonuclear leukocytes and a marked proliferative capsular reaction in many instances with a few epithelial crescents. Many glomeruli showed almost complete hyalinization. The lymph nodes showed marked phagocytic activity in the germinal centers. In

sections of the aortic arch away from the mycotic aneurysm, there was marked fibrous intimal thickening of the aorta with interruption of the elastic tissue of the media and slight perivascular infiltration with lymphocytes in the media and adventitia. A
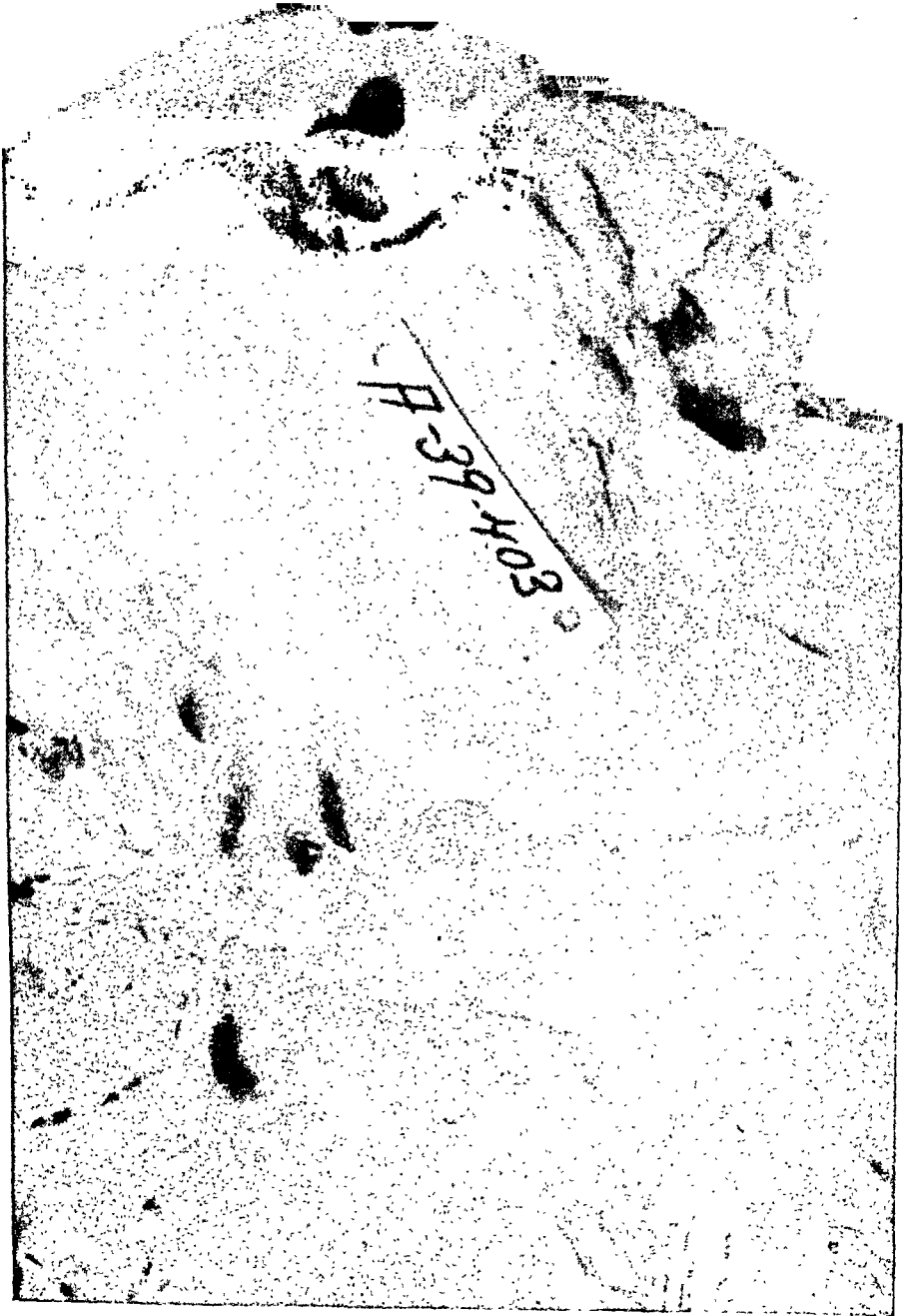
FIG. 3. Photograph of the aortic valve and aorta including the mycotic aneurysm.

section from the edge of the aneurysmal sac showed acute inflammatory infiltration consisting of polymorphonuclear leukocytes and fibrin in the intima and muscularis. There was acute necrosis involving both these areas. Rare diplococci could be seen

among the infiltrated cells. A section through the aneurysmal sac revealed complete absence of the intima and muscularis. The wall consisted of dense fibrous tissue, the surface of which was covered with young granulation tissue infiltrated by polymorphonuclear leukocytes and covered by fibrin. No elastic tissue was seen with elastic tissue stains in the aneurysmal sac. The vegetations consisted of a mass of fibrin, polymorphonuclear leukocytes and partly hyalinized material.

Bacteriology. Pneumococcus type 17 was obtained from the heart's blood. The spleen yielded gonococcus in pure culture. Vegetations from the mycotic aneurysm grew out both gonococcus and pneumococcus type 17. Cultures from the lung showed pneumococcus type 17 and *Staphylococcus aureus.*

DISCUSSION

This case is of interest from three points of view: first, as a problem in clinical diagnosis; second, as throwing some light on the problem of the causation of the Austin-Flint murmur; and, third, as an example of a rare condition, mycotic aneurysm of gonococcal origin involving a syphilitic aorta.

TABLE I

Reported Cases of Gonococcus Mycotic Aneurysm of Aorta

| Author | Date | Sex | Age | Endocarditis | | | Bacterial Endocarditis | Pericarditis | Positive Blood Culture During Life | Gonococcus Complement Fixation Test |
| | | | | Chronic Valvular Disease | | | | | | |
				Location	Type	Acute				
Holst	1901	M	24	Mitral	Rheumatic	0	0	not taken	not done
Koster	1910	M	17	0	0	0	+	not taken	not done
Thayer	1922	M	28	Aortic and mitral	Rheumatic	0	0	negative	not done
Lindau	1924	F	38	Aortic and mitral	Rheumatic	0	+	negative	not done
Riefenstein	1924	F	29	0	0	+ (aortic)	+	negative	+
Riecker	1925	M	22	+	"Mild thickening"	+ (aortic)*	0	+	not done
Thibau	1929	M	18	+	"Mild thickening"	+ (aortic)	+	+	not done
Aschner	1932	F	23	Aortic and mitral	Rheumatic	0	+	+	+
Hoyt and Warren	1938	F	28	0	0	+ (aortic)	+	negative	negative
Authors	1941	M	41	Aortic and aortitis	Syphilitic	0	0	+	+

*A single small friable vegetation on the aortic valve, which yielded a *Streptococcus hemolyticus* on culture, perhaps only a terminal lesion.

From the diagnostic angle it was considered probable that the patient was suffering from a gonococcus arthritis and the therapeutic response to sulfanilamide was thought to be to a certain extent corroborative. Gonococcus endocarditis was suspected and would have been considered as confirmed if the blood cultures had been positive during life. The etiology of the underlying heart

condition was a puzzle. A well-marked aortic diastolic murmur had been observed over a period of seven years without demonstrable cardiac enlargement. Although it did not seem probable that syphilitic aortic regurgitation could pursue such a completely benign course, this seems actually to have been the case. Whether as a result of treatment or not, the progress of the syphilitic lesion in the aorta appears to have been arrested for this prolonged period.

In this case a well-marked mitral diastolic crescendo (Austin-Flint murmur) developed under observation. It is noteworthy that this murmur developed in the absence of an increase in the transverse diameter of the heart and without recent structural change in the aortic valve. The roentgen-ray measurements of the heart shadow on January 1, 1935, showed a cardiothoracic ratio of 14.5/29.8, whereas on May 15, 1939, after the development of the murmur, it was 14.4/29.1. It is difficult therefore to explain the development of the Austin-Flint murmur on the theory of a dilated left ventricle leading to relative mitral stenosis. On the other hand, the absence of postmortem evidence of recent structural alteration in the aortic valve might seem to militate against the theory that this murmur of recent origin could be entirely ascribed to the effect of a regurgitant stream from the aorta impinging upon a mitral leaflet thus causing, in effect, a stenosis. The development of the murmur coincident with the onset of failure suggests that the altered circulatory dynamics associated with failure were responsible. Chief among these factors were an increased venous pressure and a shortened diastolic filling time (electrical systole was prolonged by 0.06 sec.).

Mycotic aneurysm is an occasional complication of bacterial invasion of the blood stream. The aorta is the artery most frequently involved but the abdominal vessels, the cerebral arteries and the arteries of the extremities are also attacked in the order named. Formation of a mycotic aneurysm is the result of lodgement of bacteria in the arterial wall with destruction of elastic fibers producing a local weakness. Aschner lists five routes by which organisms may reach the arterial wall, namely:

"(1) By direct extension from suppuration in adjoining structures, aneurysm par arrosion.

(2) By extension to or implantation upon the intima from endocarditis of the aortic cusps; endocarditis verrucosa, or ulcerosa. This may occur in a previously normal or atherosclerotic aorta.

(3) Metastatic aortitis, verrucous and ulcerous; infection by way of the blood stream implanted upon the intima from a distant focus. Here also the aorta may have been previously normal or atherosclerotic.

(4) Embolo-mycotic aortitis; embolic infection through the vasa-vasorum of the aorta by way of the coronary arteries. As bacteria may also reach the aortic wall by this route we may speak of metastatic mycotic aortitis. The source may be the heart valves or some distant focus.

(5) Lymphogenous aortitis as in cases secondary to purulent pericarditis or lymphadenitis."

It is evident that in this case the mode of development must have been as suggested under number three or metastatic ulcerative aortitis. The primary focus was not found at autopsy but it seems likely from a review of the course of the patient that the distant focus probably was the arthritis which had been present a few months before death.

SUMMARY

The reported cases of gonococcal mycotic aneurysms of the aorta are reviewed and an unusual case of a gonococcal mycotic aneurysm involving a syphilitic aorta is presented. The diagnostic difficulties encountered and certain unusual auscultatory findings are discussed.

BIBLIOGRAPHY

1. STENGEL, ALFRED, and WOLFERTH, C. C.: Mycotic aneurysms of intravascular origin, Arch. Int. Med., 1923, xxxi, 527–554.
2. ASCHNER, PAUL W.: Gonococcus aneurysms of the aorta, Libman Ann. Volumes, Vol. 1, 1932, 75–85.
3. THAYER, W. S.: On the cardiac complications of gonorrhoea, Bull. Johns Hopkins Hosp., 1922, xxxiii, 361–372.
4. LINDAU, ARVID: Aortitis gonorrhoica ulcerosa, Acta Path. et Microbiol., 1924, i, 263–275.
5. REIFENSTEIN, B. W.: Two cases of mycotic aneurysm, gonococcal and pneumococcal in origin, Am. Jr. Med. Sci., 1924, clxviii, 381–388.
6. FLINT, AUSTIN: On cardiac murmurs, Am. Jr. Med. Sci., 1862, xliv, 29–54.
7. HOYT, L. H., and WARREN, H. O.: Gonorrheal endocarditis: a report of three cases, one treated with fever therapy, ANN. INT. MED., 1938, xii, 675–687.
8. RIECKER, H. H.: Gonococcic bacteremia with gonococcic endocarditis and aortitis, Am. Heart Jr., 1925, i, 191–195.

EDITORIAL

IMMUNITY FROM INFLUENZA AND POSSIBLE METHODS FOR ITS PRODUCTION

The term influenza has been used customarily to indicate a clinical syndrome rather than a clear cut etiological entity. The usual clinical manifestations of "influenza" are familiar to all our readers: the abrupt onset with fever, malaise, prostration, generalized aches and pains, signs of irritation of the respiratory mucous membranes which are often slight in comparison with the systemic symptoms, a leukopenia and usually a high degree of contagiousness. Illness of this type may occur in great pandemics, as localized epidemics which may have a high morbidity within the area involved, and as sporadic interepidemic cases, commonly called "endemic influenza."

Definite evidence as to the etiology of influenza has been obtained only regarding a portion of the epidemic cases. Smith, Andrewes and Laidlaw [1] in 1933 first succeeded in isolating a filtrable virus by intranasal inoculation of ferrets with nasal secretion of human cases. These findings have been confirmed in many parts of the world, and there is no doubt that this virus, now designated influenza A, has been the cause of a large proportion of the cases in most of the recent epidemics which have been carefully studied. In 1940 Magill and Francis independently isolated another virus, influenza B, which serologically is entirely different from A, although the diseases they incite are otherwise indistinguishable. Finally there is a third group amounting on the average to about one-third of the epidemic cases, "influenza Y," which are not caused by either virus A or B. Nothing positive is known as to the cause of these cases, and they are best regarded as a miscellaneous aggregation which may or may not be due to one or more different viruses.

The relative frequency of these types has varied greatly in different epidemics, and all three have been found in a single epidemic. Virus A has been reported more frequently than B, but the latter was the principal cause of the epidemic in 1940, and it appears also to be widespread. It has been reported in England and in Australia.

Nothing positive is yet known as to the cause of pandemic influenza. There are many reasons for suspecting that it is caused by a virus, but this is still only an inference and it must remain so until another pandemic appears. The status of the sporadic cases is still more questionable. No virus has yet been obtained from them.

Recovery from an attack of epidemic influenza is followed by an immunity, but this is less effective and less enduring than that observed after many other virus diseases. This lack of immunity is at times more apparent

---

[1] SMITH, W., ANDREWES, C. H., and LAIDLAW, P. P.: A virus obtained from influenza patients, Lancet, 1933, ii, 66.

than real. In some individuals successive attacks have been due to. antigenically different types of virus, and no one type affords any protection from infection with any other type. Several instances have been reported, however, in which virus A was isolated in two and even three successive attacks in the same individual at about two year intervals. Minor antigenic differences between various strains of A virus have been described, but the significance of these differences is still uncertain.   ·

Studies on experimental animals (ferrets, mice) and man have furnished much information regarding the infection, although a great deal remains obscure. The present status of the problem has been well summarized by Horsfall[2] and by Francis.[3] Two discoveries of fundamental technical importance have greatly facilitated these studies. The first was the demonstration that chick embryos are highly susceptible to infection, and to a considerable extent can replace ferrets and mice for the demonstration of the virus, and even for its original isolation from patients. They also afford a convenient means of furnishing virus in large amounts and in relatively pure form.

The second was the observation of Hirst[4] that active virus causes agglutination of chicken red blood cells and that this agglutination is specifically inhibited by immune serum from man or animals. The procedure can be used for titrating the potency (antibody content) of such sera. The results are sufficiently close to those obtained by testing the protective power of the serum in mice to warrant its use in extensive epidemiological studies.

In both man and animals the portal of entry of infection is the respiratory tract. The tissue primarily attacked is the superficial ciliated epithelium, and infection is largely limited to this and to its supporting tissues. Virulent strains cause pulmonary consolidations in animals, but this is not an essential part of the disease and appears to occur rarely if at all in uncomplicated infections in man. The virus has never been found in the blood in man, and generalized systemic infection does not occur. Parenteral injections of virus do not reproduce the disease, either in man or animals. They do stimulate the development of immunity in animals, associated with the appearance of virus-neutralizing antibodies in the blood. The immunity seems to be somewhat less effective and less permanent, however, than that following recovery from infection caused by intranasal inoculation.

In man, also, recovery is accompanied by the appearance of circulating antibodies. In general the degree of protection afforded varies directly with the antibody content of the serum. In man the incidence of infection during an epidemic is greater in those with an initially low antibody titer. The

[2] HORSFALL, F. L., JR.: The present status of the influenza problem, Jr. Am. Med. Assoc., 1942, cxx, 284–287.

[3] FRANCIS, T., JR.: A rationale for studies in the control of epidemic influenza, Science, 1943, xcvii, 229–235.

[4] HIRST, G. K.: The agglutination of red cells by allantoic fluid of chick embryo infected with influenza virus, Science, 1941, xciv, 22–23.

relationship is not precise, however, and no quantity has been found which is certain to prevent infection in all individuals.

Since there is at least an approximate relationship between the virus-neutralizing power of the serum and resistance to infection, it was obviously desirable to determine whether injections of virus in man would increase the activity of the serum sufficiently to afford protection. Several extensive experiments of this type have been reported [2, 5] in which virus was administered, usually subcutaneously, a few weeks before the outbreak of an epidemic. In general there was a fairly satisfactory increase in titer of antibodies in the serum of those individuals who had had but little initially. On the other hand, if the titer was originally high, it was but little affected by the vaccination.

The results were less satisfactory, however, as far as actual protection from infection is concerned. In some series no definite reduction in the incidence of infection in the vaccinated group could be demonstrated. In others the incidence of infection was significantly reduced from the statistical standpoint, but on the average by only one-third to one-half as compared with the control groups. From the practical standpoint, this is not satisfactory.

Stokes and Henle,[5] however, reported more successful results in a group of 100 boys, of whom 72 had been vaccinated with a chick embryo virus inactivated by formaldehyde, and 28 were untreated controls. All were allowed to inhale an atomized virus suspension of considerable virulence. Ten of the controls developed clinical influenza, whereas only one case appeared in the vaccinated group. A considerable number in both groups, however, showed a slight elevation of temperature and presumably had subclinical infections.

Two factors may in part explain these relatively unsatisfactory results. The virus given may have been excessively attenuated, and the parenteral route of administration may be an unfavorable one.

The virus, in penetrating and attacking the superficial epithelium, is not directly exposed to the antibodies in the circulating blood. Antibodies presumably could protect from infection only if they were within or on the surface of the cells. Burnet studied human nasal secretion from this standpoint, and found that it had definite virus-neutralizing power, although quantitatively this was much less than that of the blood serum. Furthermore there was a direct relationship between the activity of the blood serum and that of the nasal secretion, and the latter was likewise increased by immunization. It is also reasonable to suppose that the resistance of the cells might be more effectively increased if they participated directly in the process of immunization, that is, if the virus, suitably attenuated, were administered intranasally in the hope of causing a subclinical infection. Burnet showed that this is the case in animals.

⁵ STOKES, J. JR., and HENLE, W.: Studies on methods of prevention of influenza, Jr. Am. Med. Assoc., 1942, cxx, 16–20.

Burnet[6] in 1940 reported an experiment with 17 human volunteers. An attenuated vaccine was sprayed into the nose on two occasions at one week intervals, and then an active virus was instilled into the nose and throat. Three subjects developed clinical influenza, and one other had a mild attack. Four others showed a rise in antibody titer which indicated a subclinical infection. All those who became ill had had low initial antibody titers in their serum. The attenuated virus, however, was virtually inert as it caused no rise in antibody titer except in one case.

Burnet[7] subsequently tried the effect of one nasal application of attenuated B virus in 22 volunteers. In nine cases with low initial antibody content in the serum the titer was substantially increased without any manifestation of clinical illness. He regarded this as evidence of increased resistance, but he did not report testing these cases with active virus.

Smorodintseff et al.[8] in 1937 reported the intranasal application of virus "attenuated" by passages through ferrets and mice in 72 volunteers. Of these, 14 subjects developed clinical influenza, one third had general symptoms and 40 per cent showed some nasal hyperemia and discharge. Those who developed infection all had had low initial antibody titers which rose markedly after recovery. Those with higher initial titers showed no signs of illness but may have had a subclinical infection as there was a "distinct and consistent" rise in titer, although this was less marked than in the other group.

Francis[9] has also reported applying an attenuated virus by intranasal sprays or packs without causing clinical disease but without obtaining a regular increase in circulating antibody. He did not mention direct tests for immunity in this group.

Manifestly no practicable procedure for immunization on a large scale can be mapped out on the basis of the experiments so far reported. They do suggest lines along which future experiments may be profitably conducted. If immunization is to be attempted, both A and B virus should be employed, and they should probably be administered by the intranasal route. The virus must be sufficiently attenuated so as not to cause severe infection in any appreciable number of the subjects, but it must retain sufficient activity to incite a subclinical infection in susceptible individuals. This obviously will require precise manipulation but the difficulties need not be insuperable. There appears, however, to be definite limitation to the usefulness of any immunization procedure. As already pointed out, the protection afforded by recovery from natural infection is often relatively transient, and it is not likely that better results can be obtained from any practicable method of artificial immunization. It would therefore seem to be useful

[6] BURNET, F. M., and FOLEY, M.: The result of intranasal inoculation of modified and unmodified influenza virus strains in human volunteers, Med. Jr. Australia, 1940, ii, 655–659.

[7] BURNET, F. M.: Influenza B virus. II. Immunization of human volunteers with living attenuated virus, Med. Jr. Australia, 1942, i, 673–674.

[8] SMORODINTSEFF, A. A., et al.: Investigation of volunteers infected with the influenza virus, Am. Jr. Med. Sci., 1937, cxciv, 159.

only in the face of an impending epidemic or in special situations in which even temporary protection would be important.

It is possible to secure immediate substantial although brief protection by passive immunization. Stokes and his associates have shown in animal experiments that protection can be afforded for about a ten day period by intranasal instillations of immune serum. By this route only from one-tenth to one one-hundredth as much serum is required as by parenteral injection. Smorodintseff et al.[9] have reported successful immunization by this method in man. During an extensive epidemic in Leningrad they treated 501 volunteers by intranasal administration of serum of highly immunized horses. Two doses were given at 15 day intervals. The incidence of infection was reduced from 8.2 per cent among 1825 controls to 0.4 per cent.

Such a procedure is no substitute for an effective method of active immunization. Until the latter has been perfected, however, passive immunization might be of real value, particularly in the presence of a rapidly spreading epidemic.

[9] SMORODINTSEFF, A. A. et al.: Über die spezifische Prophylaxie der epidemischen Grippe durch Inhalation antigrippösen Serums, Ztschr. f. klin. Med., 1940, cxxxviii, 756–765.

REVIEWS

Essentials of Pathology. By LAWRENCE W. SMITH, M.D., and EDWIN S. GAULT, M.D. Second Edition. 960 pages; 22.5 × 29 cm. D. Appleton-Century Co., Inc., New York. Price, $10.00.

This book on pathology as its name indicates is primarily designed to meet the needs of medical students and practitioners. It is not recommended for workers in the specialized field of pathology, since there are many volumes written on subjects which can only briefly be discussed in this text. Nevertheless it contains an excellent bibliography.

In general the orthodox and familiar arrangement of discussion is followed: (1) general pathology, (2) tumors, and (3) systemic pathology. This is in reality a handbook of pathology plus an atlas, and contains many excellent photographs and plates. In this second edition the first thirteen chapters which deal with fundamental pathological changes has been given more elaboration and space.

There are 295 complete case histories presented. The case history method of presentation and correlation of clinical and pathological changes is especially useful for the student. The microscopic descriptions are of great value in laboratory work. This method is not entirely new in textbooks on pathology since it was used by W. T. Councilman in 1912.

The book is larger than average and not of convenient size. Many blank pages are inserted for additional notes. Value of these pages is questionable as many book lovers are hesitant to mark up their valuable books. Also the margins are rather wide and add to the size of the volume.

The subject material on the whole is very well presented. The parasitic infestations are given adequate space. This is of especial importance now, and will be for some time to come because of the war and greater development in rapid transportation.

B. S.

BOOKS RECEIVED

Books received during May are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Aviation Medicine. By LOUIS HOPEWELL BAUER, M.D. Edited by HENRY A. CHRISTIAN, A.M., M.D., LL.D., Sc.D. (Hon.), F.A.C.P., Hon. F.R.C.P. (Can.). 50 pages; 24 × 16 cm. 1943. Oxford University Press, New York City. Price, $1.50.

Gout. By JOHN H. TALBOTT, M.D. Edited by HENRY A. CHRISTIAN, A.M., M.D., LL.D., Sc.D. (Hon.), F.A.C.P., Hon. F.R.C.P. (Can.). 55 pages; 24 × 16 cm. 1943. Oxford University Press, New York City. Price, $2.50.

Medico-Legal Blood Group Determination. Theory, Technique, and Practice. By DAVID HARLEY, M.D., B.Sc., F.I.C. 119 pages; 22.5 × 15 cm. 1943. Grune & Stratton, Inc., New York City. Price, 12's. 6 d. net.

Clinical Roentgenology of the Cardiovascular System. Second Edition. By HUGO ROESLER, M.D., F.A.C.P. 480 pages; 26 × 17 cm. 1943. Charles C. Thomas, Springfield, Illinois. Price, $7.50.

Allergy, Anaphylaxis and Immunotherapy. By BRET RATNER, M.D. 834 pages; 23.5 × 16 cm. 1943. Williams and Wilkins Co., Baltimore. Price, $8.50.

The Physiological Basis of Medical Practice. Third Edition. By CHARLES HERBERT BEST, M.A., M.D., D.Sc. (Lond.), F. R. S., F.R.C.P. (Canada), and NORMAN BURKE TAYLOR, M.D., F.R.S. (Canada), F.R.C.S. (Edin.), F.R.C.P. (Canada), M.R.C.S. (Eng.), L.R.C.P. (Lond.). 1942 pages; 23.5 × 16 cm. 1943. Williams and Wilkins Co., Baltimore. Price, $10.00.

Your Arthritis. What You Can Do About it. By ALFRED E. PHELPS, M.D. With an Introduction by R. GARFIELD SNYDER, M.D. 192 pages; 19.5 × 13 cm. 1943. William Morrow & Co., Inc., New York City. Price, $2.00.

Essentials of Syphilology. By RUDOLPH H. KAMPMEIER, A.B., M.D. 518 pages; 20 × 13.5 cm. 1943. J. B. Lippincott Co., Philadelphia. Price, $5.00.

Skin Grafting of Burns. By JAMES BARRETT BROWN, M.D., and FRANK McDOWELL, M.D. (Lt. Col., Med. Corps, A.U.S.). 204 pages; 26.5 × 18.5 cm. 1943. J. B. Lippincott Co., Philadelphia. Price, $5.00.

Vitamins and Hormones. Vol. I. (*Advances in Research and Applications.*) Edited by ROBERT S. HARRIS and KENNETH V. THIMANN. With a foreword by E. V. McCOLLUM. 452 pages; 23.5 × 15.5 cm. 1943. Academic Press, Inc., New York City. Price, $6.50.

A Guide to Practical Nutrition. A series of articles on nutrition, sponsored by the Committee on Nutrition and Deficiency Diseases of the Philadelphia County Medical Society. Reprinted from Philadelphia Medicine, 1941–1942. Edited for the Committee by MICHAEL G. WOHL, M.D., and JOHN H. WILLARD, M.D. Introduction by MORRIS FISHBEIN, M.D. 98 pages; 24.5 × 17 cm. 1943. Philadelphia County Medical Society, Philadelphia.

COLLEGE NEWS NOTES

Already published in preceding issues of this journal were the names of 1,430 Fellows and Associates of the College on active military duty. Herewith are reported the names of 10 additional members, bringing the grand total to 1,440.

Marvin B. Corlette
Dolph L. Curb
Thomas H. DeLaureal
Harold Fink
Marshall W. Graham

Saul Jarcho
Robert M. Lintz
E. David Sherman
Brandt F. Steele
William D. Stubenbord

TENTATIVE PROGRAM OF POSTGRADUATE COURSES OF THE AMERICAN COLLEGE OF PHYSICIANS, AUTUMN, 1943

In accordance with the policy of the College in furnishing to its members and medical officers in the armed forces opportunities for graduate instruction, the Advisory Committee on Postgraduate Courses has announced the following program for the autumn of 1943:

Course No. 1. ENDOCRINOLOGY (October 11–16) at Chicago under the directorship of Dr. Willard O. Thompson, F.A.C.P.; Fee, $20.00.
Course No. 2. ALLERGY (October 25–30) at Roosevelt Hospital, New York City, under the directorship of Dr. Robert A. Cooke, F.A.C.P.; Fee, $20.00.
Course No. 3. SPECIAL MEDICINE (November 8–19) at various Philadelphia institutions under the directorship of Dr. Charles L. Brown, F.A.C.P.; Fee, $40.00.

Course No. 3, Special Medicine, will be an unusual course in that it will be given, not at a single institution, but at most of the leading medical institutions in Philadelphia, including special days and special subjects at Temple University School of Medicine, University of Pennsylvania School of Medicine and Graduate School of Medicine, the Pennsylvania Hospital, Jefferson Medical College of Philadelphia, the Phipps Institute, the Philadelphia General Hospital, the Institute of the Pennsylvania Hospital, the Lankenau Hospital, the Hospital of the University of Pennsylvania, and the Philadelphia City Morgue. Subjects covered will include psychosomatic medicine, allergy, arthritis and related conditions, blood diseases, cardiovascular diseases, peripheral diseases, syphilis, gonorrhea, respiratory diseases, tuberculosis, gastrointestinal diseases, chemotherapy, diagnostic roentgenography, psychiatry, metabolic problems, tropical medicine, tumors, and legal medicine.

The course will conclude on Friday, November 19, which will be devoted to a Regional Meeting of the College for Pennsylvania, New Jersey, Delaware, and adjacent territories. Members of the College committees and the Board of Regents will be present to take part in the Regional Meeting, which will include, in the morning, medical clinics at the Hospital of the University of Pennsylvania under Dr. O. H. Perry Pepper, F.A.C.P.; at noon, a buffet luncheon at the College Headquarters; in the afternoon, a general session with papers by eminent authorities; and, in the evening, a social hour and dinner meeting at one of Philadelphia's leading hotels.

Gifts to the College Library

We gratefully acknowledge receipt of the following gifts to the College Library of Publications by Members:

Reprints

Dr. Lyman B. Carruthers, F.A.C.P., Miraj, S.M.C., India—3 reprints;
Dr. Harold R. Carter (Associate), Denver, Colo.—1 reprint;
Dr. Herbert R. Edwards, F.A.C.P., New York, N. Y.—13 reprints; ·
Jack D. Kirshbaum (Associate), Major, (MRC), U. S. Army—19 reprints;
Dr. Vincent W. Koch, F.A.C.P., Janesville, Wis.—1 reprint;
Aleksei A. Leonidoff, F.A.C.P., Lieutenant Colonel, (MRC), U. S. Army—1 reprint;
Benjamin H. Neiman (Associate), Major, (MRC), U. S. Army—1 reprint;
Frank B. Queen, F.A.C.P., Lieutenant Colonel, (MRC), U. S. Army—1 reprint;
Dr. David Salkin, F.A.C.P., Hopemont, W. Va.—1 reprint;
Dr. Leon Schiff, F.A.C.P., Cincinnati, Ohio—1 reprint;
Dr. Leon Schwartz, F.A.C.P., Medical Officer of the Bureau of Census—"The Health Program of the United States Bureau of the Census";
Dr. R. S. Anderson, F.A.C.P., Erie, Pa.—"Annual Report for 1942 of the Erie County Tuberculosis Hospital."

Southeastern States Regional Meeting

The American College of Physicians held a Regional Meeting at Jacksonville, Fla., May 26, 1943, for the States of Florida, Georgia, Alabama and South Carolina. The program has been published in a previous issue of this journal. An analysis of the attendance showed a total of 146, of whom 84 were Service physicians and 62 were civilian physicians. Of this number, however, 72 were members of the College, and 74 were guests, chiefly from the Medical Corps of the Army and Navy in the district. The member attendance was 23.9 per cent for the territory, which, though considerably lower than the average for Regional Meetings which heretofore has been about 40 per cent, was nevertheless a good showing, due to the acute war conditions in that part of the country.

The scientific program was held throughout the morning and afternoon, with the respective State Governors presiding at different sessions. In the evening there was a social hour from six-thirty, and a dinner at the George Washington Hotel at seven-thirty, at which Dr. T. Z. Cason, Governor for Florida, was the Toastmaster. Addresses were made at the dinner-meeting by Dr. Ernest E. Irons, President-Elect of the College, Chicago, Ill.; Rear Admiral Dallas G. Sutton, Envoy of the Surgeon General of the U. S. Navy, Washington, D. C.; Colonel Henry M. Thomas, Jr., Envoy of the Surgeon General of the U. S. Army, Atlanta, Ga.; Dr. Charles H. Cocke, First Vice President of the College, Asheville, N. C.; and Edward R. Loveland, Executive Secretary of the College, Philadelphia, Pa. Among other special guests at the dinner-meeting were Colonel Charles B. Callard, Director of the Medical Division, Camp Blanding, Fla., and Captain John J. O'Malley, Commanding Officer of the U. S. Naval Hospital, Naval Air Station, Jacksonville, Fla.

The annual dinner meeting of the Mississippi members of the American College of Physicians was held Tuesday, May 11, 1943, in Jackson during the annual meeting of the Mississippi State Medical Association. The dinner was well attended by mem-

bers of the College and their wives.   Dr. John G. Archer, F.A.C.P., College Governor for Mississippi, Greenville, presided and the following Fellows of the College participated in the program:

  Dr. G. W. F. Rembert, Jackson—"Some High Lights on the By-Laws of the American College of Physicians";
  Dr. Douglas D. Baugh, Columbus—"Ways and Means of Increasing the Mississippi Membership in the American College of Physicians";
  Dr. Laurance J. Clark, Vicksburg—"Some Remarks";
  Dr. Wesley W. Lake, Pass Christian—"Report of a Case of Plummer Vinson's Syndrome."

  Dr. Edgar Hull, F.A.C.P., College Governor for Louisiana, New Orleans, was the guest speaker.   Dr. Hull spoke on "The Prospect of Public Medicine."

———

  Dr. Homer E. Prince, F.A.C.P., Houston, spoke on "Bronchial Asthma" at a meeting of the medical students of the University of Texas Medical Branch, Galveston, May 12, 1943.

———

  The 8th Annual Meeting of the National Gastroenterological Association was held in New York, N. Y., June 3, 1943, under the Presidency of Dr. Anthony Bassler, F.A.C.P., New York, N. Y.   Among those who participated in the discussions and activities of the convention were Dr. Samuel Weiss, F.A.C.P., Dr. Max Einhorn, F.A.C.P., Dr. Thomas H. McGavack, F.A.C.P., and Dr. Henry A. Rafsky, F.A.C.P., all of New York, N. Y., Michael Lake, F.A.C.P., Lieutenant Commander, (MC), U. S. Naval Reserve, Dr. Louis L. Perkel, F.A.C.P., Jersey City, N. J., Dr. Sigurd W. Johnsen, F.A.C.P., Passaic, N. J., Henry A. Monat (Associate), Lieutenant Commander, (MC), U. S. Naval Reserve, and Dr. Hyman I. Goldstein (Associate), Camden, N. J.

———

  Dr. Fred W. Wilkerson, F.A.C.P., Montgomery, has been elected President of the Medical Association of the State of Alabama.

———

  Dr. Louie Limbaugh, F.A.C.P., Jacksonville, has been named one of the Vice Presidents of the Florida Medical Association.

———

  At a regional meeting of the American College of Surgeons in Charlotte, N. C., March 22, 1943, addresses were made by Dr. Robert Wilson, Sr., F.A.C.P., Charleston, former College Governor for South Carolina, and Dr. Charles H. Cocke, F.A.C.P., Asheville, First Vice President of the College.

———

  At the 90th Annual Meeting of the North Carolina State Medical Society held in Raleigh, May 11–13, 1943, Dr. James W. Vernon, F.A.C.P., Morganton, was installed as President and Dr. Paul F. Whitaker, F.A.C.P., Kinston, was named President-Elect.

The Press Division of the Coördinator of Inter-American Affairs is republishing in Spanish the book, "Health Officer's Manual" by Dr. Jacob C. Geiger, F.A.C.P., Director of Public Health of the City and County of San Francisco. The book has been translated by Dr. Osvaldo Cifuentes, who proposes to publish it under his direction as a publication of the Direccion General de Sanidad of the Chilean Government.

On May 22, 1943, at its commencement exercises, Duke University conferred the honorary degree of Doctor of Science on James S. Simmons, F.A.C.P., Brigadier General, (MC), U. S. Army, Director of the Preventive Medicine Division, Office of the Surgeon General.

On May 21, 1943, Dr. J. Arnold Bargen, F.A.C.P., Rochester, Minn., spoke on "The Varieties of Ulcerative Colitis" at a meeting of the Delaware Academy of Medicine at Wilmington.

The Association of Military Surgeons of the United States will hold its 51st annual convention in Philadelphia, October 21–23, 1943. This meeting will assemble physicians from all of the current war fronts where United States forces are fighting and from all the great base hospitals where rehabilitation of the wounded is in progress. Numerous forum lectures, practical demonstrations, motion pictures and teaching panels will be conducted to present the latest techniques of wartime medicine and surgery.

Ross T. McIntire, F.A.C.P., Rear Admiral, (MC), U. S. Navy, The Surgeon General, is the Honorary Chairman of this meeting, Joseph A. Biello, Captain, (MC), U. S. Navy, General Chairman; and George F. Lull, F.A.C.P., Brigadier General, (MC), U. S. Army, and Edward L. Bortz, F.A.C.P., Commander, (MC), U. S. Naval Reserve, are Vice-Chairmen.

The Executive Committee includes Captain R. H. Laning, (MC), U. S. Navy, Commanding Officer of the Philadelphia Naval Hospital, Dr. Stanley P. Reimann, F.A.C.P., Philadelphia, Dr. Gilson Colby Engel, Philadelphia, Commander J. L. Tinney, (M.C), U. S. Naval Reserve, and Dr. A. Newton Richards, Philadelphia, Vice President of the University of Pennsylvania.

Dr. Robert U. Patterson, F.A.C.P., Dean of the University of Maryland School of Medicine, Baltimore, has been appointed Consultant to the Baltimore City Health Department.

Dr. Herbert A. Burns, F.A.C.P., Minneapolis, Minn., has been placed in charge of the new Tuberculosis Control Unit in the State Division of Public Institutions.

Dr. V. P. Sydenstricker, F.A.C.P., Augusta, Ga., delivered the Eighth Harvey Society Lecture at the New York Academy of Medicine, New York, N. Y., May 20, 1943. Dr. Sydenstricker spoke on "Nutrition under Wartime Conditions."

Dr. Reginald Fitz, F.A.C.P., Boston, Mass., will speak on "The Crimson Thread" on a special program commemorating the one hundredth anniversary of the founding of Western Reserve University School of Medicine, Cleveland, Ohio, October 27, 1943.

Dr. David W. E. Baird, F.A.C.P., has been appointed Dean of the University of Oregon Medical School, Portland.

At a joint meeting of the Sixth and Seventh Councilor Districts of the Medical Society of the State of Pennsylvania, held in Williamsport, May 14, 1943, Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, spoke on "The Modern Science of Nutrition and Nutritional Deficiency" and Dr. Walter F. Donaldson, F.A.C.P., Pittsburgh, spoke on "War Participation and Organized Medicine."

Walter S. Jensen, F.A.C.P., Colonel, (MC), U. S. Army, Executive Officer in the Office of the Air Surgeon, delivered the annual Edwin J. Jarecki Memorial Lecture in Philadelphia, Pa., April 29, 1943.

Among the speakers at the annual meeting of the Iowa and Illinois Central District Medical Association held in Rock Island, Ill., May 27, 1943, were:

Dr. Italo F. Volini, F.A.C.P., Chicago, Ill.—"Clinical Observations on Heart Disease";

Dr. Charles F. McKhann, F.A.C.P., Ann Arbor, Mich.—"Progress in the Control of Communicable Disease."

Dr. Clarence E. de la Chapelle, F.A.C.P., Professor of Clinical Medicine at New York University College of Medicine, has been named Acting Assistant Dean of the University.

Dr. Titus H. Harris, F.A.C.P., Galveston, has been elected President of the Texas Association for Mental Hygiene.

Dr. Horace M. Banks, F.A.C.P., and Dr. Harold F. Dunlap, F.A.C.P., both of Indianapolis, discussed a "Case of Sarcoidosis" at the annual session of the American Society of Clinical Pathologists held in Chicago, Ill., June 3–6, 1943.

Dr. Thomas H. A. Stites, F.A.C.P., has resigned as Medical Director of the Pennsylvania State Tuberculosis Sanatorium, Cresson.

Under the Presidency of Dr. Karl J. Henrichsen, F.A.C.P., Chicago, Ill., the American Academy of Tuberculosis Physicians held its annual meeting in Chicago, June 9–10. One of the guest speakers was Dr. David Salkin, F.A.C.P., Hopemont, W. Va., who spoke on the "Treatment of Tuberculous Bronchitis."

Dr. John W. Wilce, F.A.C.P., Columbus, Ohio, has been named representative of the Ohio State Medical Association on the State Advisory Committee on Recreation and Physical Education, which is supervising the Ohio Physical Fitness Program for the Department of Education.

Dr. Chester W. Waggoner, F.A.C.P., Toledo, Ohio, has been reappointed a member of the Ohio Medical Board for the term ending March 18, 1950.

Dr. Oswald F. Hedley, F.A.C.P., U. S. Public Health Service, Bethesda, Md., addressed the Rhode Island Industrial Health Institute held in Providence, May 19, 1943. Dr. Hedley spoke on "What the Average Plant Can Do to Have an Industrial Health Program."

The annual meeting of the American College of Radiology was held in Chicago, Ill., June 6, 1943, under the Presidency of Dr. Byrl R. Kirklin, F.A.C.P., Rochester, Minn. The College sponsored a Conference of Teachers of Clinical Radiologists. During this conference Edward L. Bortz, F.A.C.P., Commander, (MC), U. S. Naval Reserve, discussed "War-time Graduate Medical Meetings."

Dr. George Baehr, F.A.C.P., Chief Medical Officer, Office of Civilian Defense, Washington, D. C., recently conferred with Mexican civilian defense officials in Mexico City on their organizational problems. While in Mexico City, Dr. Baehr spoke on "The Organization and Operation of the Emergency Medical Service" and discussed "Rescue Service."

Dr. Edward P. Eglee, F.A.C.P., New York, N. Y., has been named Chairman, and Dr. Charles H. Cocke, F.A.C.P., Asheville, N. C., Dr. George B. Gilbert, F.A.C.P., Colorado Springs, Colo., Dr. Alvis E. Greer, F.A.C.P., Houston, Tex., Dr. Foster Murray, F.A.C.P., Brooklyn, N. Y., and Dr. J. J. Singer, F.A.C.P., Los Angeles, Calif., members of the Council on Postgraduate Medical Education of the American College of Chest Physicians.

On February 10, 1943, Sharp and Dohme, Inc., of Philadelphia, received the Army-Navy "E," for excellence in production. Both the pharmaceutical and biological laboratories received the award. This was presented on behalf of the Army by Brigadier General Hugh J. Morgan, M.C., F.A.C.P., and for the Navy by Commander Edward L. Bortz, M.C., F.A.C.P. The award is well deserved, particularly for the pioneer work of this firm in developing practicable methods for the preparation of dried blood plasma on a large scale.

Dr. Edward A. Strecker, F.A.C.P., Philadelphia, Pa., President of the American Psychiatric Association, has been appointed Special Consultant to the Secretary of War for the Air Forces of the U. S. Army. Dr. Strecker is also Consultant in Psychiatry to the Surgeon General of the U. S. Navy. For some time, Dr. Strecker has been giving intensive training in psychiatry to Naval Medical Officers in Philadelphia. All of the medical and hospital facilities in this field are coöperating in the program, three months in length. In World War I he served as Major in the Army Medical Corps, as Division Neuropsychiatrist for the 28th Division in France.

Dr. Strecker is Professor and Head of the Department of Psychiatry of the Graduate School of Medicine and in the Medical School of the University of Pennsylvania. Since 1917, he has been Medical Director of the Pennsylvania Hospital

Department of Nervous and Mental Diseases. He is Chief of Service at the Institute for Mental Hygiene of the Pennsylvania Hospital and Consultant to Bryn Mawr College and the U. S. Veterans Bureau.

The Omaha Mid-West Clinical Society will hold its eleventh annual assembly October 25–29 at the Hotel Paxton, Omaha, Nebraska.

Among the speakers who have accepted places on the program are Dr. James E. Paullin, F.A.C.P., Atlanta, Ga.; Dr. Tom D. Spies, F.A.C.P., Birmingham, Ala.; Dr. Harold G. Wolff, F.A.C.P., New York, N. Y.; Dr. Eben J. Carey, Milwaukee, Wis.; Dr. Sanford R. Gifford, Chicago, Ill.; Dr. L. Emmett Holt, Jr., Baltimore, Md.; Dr. Frank R. Ober, Boston, Mass.

Friday, October 29, will be devoted to a symposium on "War Medicine and Surgery." The participants will be physicians of the United States Naval Medical Corps. There will also be other periods in the program devoted to problems confronting the Medical Corps of the United States Army. Scientific and technical exhibits, along with a moving picture program, will complete a five-day meeting.

OBITUARIES

DR. CLAUDE W. ASHLEY

Dr. Claude W. Ashley, F.A.C.P., Bloomsburg, Pa., born February 2, 1905, died suddenly on May 22, 1943.

Dr. Ashley was born in St. Louis, Missouri, and graduated from the William Jewell College in Missouri, in 1928. He received his degree of Doctor of Medicine from Jefferson Medical College of Philadelphia in 1932.

For two years, Dr. Ashley served as Resident in Pediatrics at the Children's Hospital in Cincinnati, and from 1934 to 1935 he was Resident in Internal Medicine at the Geisinger Memorial Hospital in Danville, Pennsylvania.

Dr. Ashley has been outstanding in the medical activities of his community and has been a true servant of his profession throughout the short time of his practice. At the time of his death, he was Chief of the Medical Service, Chief Pediatrician and Vice President of the Staff of the Bloomsburg Hospital. He was a Diplomate of the National Board of Medical Examiners and also a Diplomate of the American Board of Pediatrics. Dr. Ashley also served as former Secretary and President of the Columbia County Medical Association.

Medical society memberships included the Pennsylvania State Medical Society, Fellowship in the American Medical Association and Fellowship in The American College of Physicians.

Dr. Ashley's untimely death has come as a great shock to his many friends and colleagues and it is with sincere regret that we acknowledge his passing.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. GEORGE B. LAKE

Dr. George B. Lake (Associate) was born in Topeka, Kansas, November 26, 1880, and died in the Lake Forest Hospital, Lake Forest, Illinois, March 2, 1943.

He received his formal education at Wheaton College, the University of Michigan, and graduated from Rush Medical College in 1902. The next two years he spent as Assistant Surgeon of the Mexican Central Railway Hospital. It was probably during this time that he acquired command of the Spanish language. From 1908 to 1910 he was special lecturer in Rural Hygiene and Sanitation at Purdue University.

In 1910 he entered the Medical Corps of the U. S. Army. He graduated from the Army Medical School in 1911 and took part in the Philippine campaign in 1913. He was on General Pershing's staff during the invasion of Mexico and was selected as one of the force of specially picked men who

left the main body of the army to make a grilling and hazardous dash after the bandit Villa. He served in the Medical Corps until 1924 and resigned with the rank of Major. Later he became a Colonel in the Medical Reserve Corps of the Army.

In 1924 he assumed editorship of the journal which later became Clinical Medicine and Surgery, and in 1934 he became editor and publisher of that journal.

He was a poet of considerable ability and published a number of volumes of poems. At one time he was President of the London Poetry Society.

He was interested in mysticism, philosophy, psychiatry and metaphysics. He was deeply religious and was a priest of the Liberal Catholic Church and often conducted services in the Church of St. Francis in Chicago.

He was a member of the Chicago Medical Society; the Illinois State Medical Society; the Mississippi Valley Medical Society; the Association for the Study of Internal Secretions; the American Association of the History of Medicine; the Association of Military Surgeons of the United States; the Mississippi Valley Medical Editors' Association, of which he was President during 1941; and a Fellow of the American Medical Association. Dr. Lake was a member of the American Congress on Internal Medicine and became an Associate of the American College of Physicians when the College and the Congress merged.

His philosophy of life gave him tranquillity and joy beyond the experience of most men.

JAMES H. HUTTON, M.D., F.A.C.P.,
Chicago, Ill.

DR. ARTHUR E. DAVIS

Dr. Arthur E. Davis, Scranton, Pennsylvania, died at his home on May 2, 1943, after an illness of one week.

Dr. Davis was born at Avoca, Pennsylvania, on March 25, 1887. He attended Hillman Academy and graduated in medicine from the Medico-Chirurgical College of Philadelphia in 1911.

He was, for many years, Visiting Chief at the West Side and Scranton State Hospitals, and Cardiologist at the Mercy Hospital. Dr. Davis was former President of the Lackawanna County Medical Society; he held membership in the Pennsylvania State Medical Society and the American Medical Association. Since 1928, he has been a Fellow of the American College of Physicians.

The sudden death of Dr. Davis has come as a great shock to his many friends and colleagues throughout the entire State. He has been held in high esteem as an internist of renown and it is with a deep sense of loss that his passing is acknowledged.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. ALBERT HAMMOND HOGE

Dr. Albert Hammond Hoge was born at Hoge's Store, Giles County, Virginia, August 17, 1885, the son of Samuel S. and Mary Price Hoge. After graduating from Mayfield High School he entered Massey College, Richmond, Va., in 1903. The next year he matriculated at the University College of Medicine, Richmond, where he graduated in 1908. After graduation he served a year's internship at St. Luke's Hospital, Richmond. In the fall of 1909 he located in Bluefield, W. Va., where he became associated with Dr. Charles M. Scott in the management of St. Luke's Hospital, where he remained continuously, being Medical Director at the time of his death.

Dr. Hoge early in his professional career became an outstanding physician and a leader in organized medicine. He served as president of the Mercer County Medical Society and in 1932 was president of the West Virginia State Medical Association. He was a Fellow of the American Medical Association, and in 1924 he was elected to Fellowship in the American College of Physicians. In 1939 he became a member of its Board of Governors. In 1930 Governor Conley appointed Dr. Hoge to membership on the West Virginia Public Health Council which combines the functions of both a state board of health and a state board of medical examiners. He was a member of this body for twelve years, served as president from 1933 to 1937. Dr. Hoge was a Diplomate of the American Board of Internal Medicine.

A convincing speaker and a lucid writer, he was the author of numerous articles on medical subjects. Strangely enough, his last article was the obituary of Dr. Charles W. Waddell, published in the May issue of the ANNALS, which was received by the Philadelphia office after Dr. Hoge's death. Shortly after graduation he was elected to membership in the Medical Society of Virginia, which membership he very appropriately maintained until his death inasmuch as he resided very close to the state line and drew a large clientele from both his native and adopted states.

Not only was Dr. Hoge an outstanding physician but he was an outstanding citizen. He was a Mason and a Shriner, a past president of the Bluefield Rotary Club, and an official of the Community Savings and Loan Association. In company with his brothers, he operated his large ancestral estate in Giles County as a stock and apple farm. He served in the Army Medical Corps in World War I. He was in faith a Presbyterian and in politics a Democrat. His friends were legion throughout both the Virginias. He was an ardent devotee of both rod and gun and one of the best shots in the entire South.

Shortly before midnight on April 7, Dr. Hoge suffered a very severe coronary occlusion and died in an ambulance en route to the hospital. A fortnight before he had been slightly indisposed but he felt he had recovered and had worked regularly the last few days preceding his sudden fatal attack.

West Virginia has lost an outstanding citizen and the medical profession a stalwart member.

<div align="right">

WALTER E. VEST, M.D., F.A.C.P.,
Governor for West Virginia

</div>

DR. ANDREW SLOAN

Dr. Andrew Sloan (Fellow, 1922) was born in Utica, N. Y., January 5, 1880, with a professional background which assured him scientific acumen and high ethical principles, for his father, Dr. Hugh Sloan, had been an outstanding physician of a generation now past and his mother, Elizabeth Wetzel Sloan, was the daughter of a Lutheran clergyman whose memory is still green among the older citizens of the community.

Andrew Sloan, upon being graduated by the Utica Free Academy, studied medicine at the College of Physicians and Surgeons of Columbia University and was graduated there in 1902. For the past forty-one years he has been a practicing physician as an internist in Utica, particularly interested in hospital administration.

On the retirement of Dr. Willis Ford as Medical Director of St. Luke's Hospital in 1921, Dr. Sloan was his logical successor and immediately assumed the position which he held for more than a decade. His influence was manifest in the hospital and to him is due to no small extent the high medical and ethical standing of that institution. When the Utica Visiting Nurses and Child Health Association was formed Dr. Sloan became chairman of the Medical Advisory Board. The growth of this potent civic institution during the past fifteen years is a measure of his efficiency and public service spirit.

In 1921 Dr. Sloan became vice-president of the Medical Society of the County of Oneida and the following year its president. The Medical Society of the State of New York recognized his services in its House of Delegates over many years by electing him First Vice-President and sending him as a delegate to the American Medical Association.

Dr. Sloan was also a past president of the Utica Medical Club, a member of the Fort Schuyler and Yahnundasis Clubs, and of the Masonic Fraternity.

Dr. Sloan will be long remembered as the founder and, for its first ten years, the president of the Utica Academy of Medicine. Here his enthusiasm, his professional zeal, and his insistence that the Academy should maintain the highest standards and become a post-graduate school for his fellow physicians of the Mohawk Valley, launched the Academy on a career of great usefulness to its members and influence throughout New York State.

He leaves a wife, Margaret Diefenbach Sloan, and three brothers, Hugh Sloan, Samuel Sloan and Dr. Robert Sloan, a past president of the Oneida County Medical Society.

<div align="right">

WILLIAM A. GROAT, M.D., F.A.C.P.,
Syracuse, N. Y.

</div>

DR. JOHN HYREN PECK

Dr. John Hyren Peck, F.A.C.P., was born at Lost Nation, Iowa, August 3, 1879; he died at his home at Oakdale, Iowa, October 18, 1942, of coronary thrombosis.

Dr. Peck attended the public schools of Olin, Iowa, and the State University of Iowa, from which he received the degree of M.D. in 1909. Following an internship at the State University of Iowa, he entered the practice of medicine in Des Moines. He developed an early interest in diseases of the chest, and in 1912 served as resident physician in the State Sanatorium at Oakdale, after which he resumed practice in Des Moines. In 1936, he became superintendent of the State Sanatorium.

Dr. Peck served as president of the Polk County Medical Society, the Iowa State Medical Society, the National Tuberculosis Association, and the American College of Chest Physicians; he was president of the Iowa Tuberculosis Association from 1918 to 1934. He became a Fellow of the American College of Physicians in 1930. During World War I, he served as a Major in the U. S. Army Medical Corps, and was chief of the tuberculosis service at the base hospital at Camp Dodge. He was certified by the American Board of Internal Medicine.

The most unique, and possibly the most fruitful feature of Dr. Peck's professional career was his educational activity in the field of tuberculosis. Almost single-handedly, he made the State of Iowa, medical and lay, tuberculosis conscious. For twenty years, in addition to caring for a busy practice, he conducted diagnostic clinics and gave addresses on tuberculosis in every county in the State. He knew nearly every physician in the State by his first name, and was regarded affectionately by all of them. He well deserved the high honors which came to him.

<div style="text-align: right">B. F. WOLVERTON, M.D., F.A.C.P.,
Governor for Iowa</div>

DR. JOHN TAYLOR WATKINS

Dr. John Taylor Watkins, F.A.C.P., Detroit, Mich., died of cerebral hemorrhage, May 8, 1943.

Born in Whitmore Lake, Michigan, in 1883; he graduated from the University of Michigan Medical School in 1906. After one year of general practice in the Upper Peninsula of Michigan, he moved to Detroit, where he later confined his work to Internal Medicine. Until ill health necessitated his retirement six and one half years ago, Dr. Watkins enjoyed a large and select practice in his chosen field. An able clinician, he had those personal characteristics that inspired confidence and endeared him to his patients. Meticulous in dress, scholarly in diction, gentle and dignified in manner, he radiated that professional atmosphere that all admire but few possess.

During his active career he was honored with the following appointments and memberships: Professor of Clinical Medicine at the Detroit College of Medicine and Surgery, now Wayne University College of Medicine; Physician-in-Chief and Vice Chief of Staff to the Grace Hospital; Chief of Staff at the Woman's Hospital; Consulting Physician to the Highland Park General Hospital; member of the Wayne County Medical Society, Michigan State Medical Society, American Medical Association, the American Therapeutic Society and had been a Fellow of the American College of Physicians since 1920.

Besides his immediate family and relatives he leaves a host of friends, both lay and professional. It is with deep regret that we mark his passing.

P. L. Ledwidge, M.D., F.A.C.P.,
Acting Governor for Michigan

STUDIES OF URINARY PIGMENTS IN PELLAGRA AND OTHER PATHOLOGICAL STATES. I. CLINICAL OBSERVATIONS [*]

By CECIL JAMES WATSON, M.D., F.A.C.P., and JOHN A. LAYNE, M.D., *Minneapolis, Minnesota*

IN previous communications,[1, 2] one of us (C. J. W.) pointed out that the Ellinger-Dojmi color reaction [3] is due to urorosein, and that porphyrin, although capable of yielding color if present in sufficient amount, was not the source of the positive reactions encountered in urine samples from a variety of conditions, including pellagra. Beckh, Ellinger and Spies [4] had employed the Ellinger-Dojmi reaction for the quantitative estimation of porphyrin in the urine. These investigators reported marked increases of porphyrin in a series of pellagra urines. They stated, moreover, that the administration of nicotinic acid was followed by a prompt fall in the excretion of urinary porphyrin to normal levels. Similar observations were subsequently reported by Sydenstricker, Schmidt, Fulton, New and Geeslin [5] and by Spies and various associates,[6, 7, 8] although in later publications by Spies [9, 10, 11] the pigments responsible for the color reactions were referred to as "porphyrin-like substances." Dobriner and Rhoads [12] and Meiklejohn and Kark [13] have also attested to the non-specificity of the Ellinger-Dojmi reaction for porphyrin, and the latter investigators confirmed the report of Watson [2] that the reaction occurring in pellagra urines. is due to urorosein. As a matter of fact, Hunter, Givens, and Lewis [14] in 1919 had noted that urorosein was commonly present in the urine of pellagrins. Since the urorosein reaction may occur in certain urines only after the addition of an oxidizing agent,[2, 13] further investigation was necessary to determine whether the presence of this pigment was correlated in any direct manner with nicotinic acid deficiency.

In addition to positive urorosein reactions, Watson [1, 2] described a red

pigment resembling indirubin, occurring in the toluene preservatives of urines from pellagrins as well as other patients having deficiency states.

The present study was concerned with the urinary excretion of urorosein and indirubin, or indirubin-like substances in normal human subjects and in patients with nicotinic acid deficiency. Similar studies have also been made of the urine of patients suffering from pathological conditions without clinical evidence of nicotinic acid deficiency.

METHODS AND MATERIALS

Urines of eight patients presenting definite clinical evidence of nicotinic acid deficiency were examined daily for the urorosein reaction, for indican, for the presence of an oxidizing agent, and for the development of a red color in the toluene preservatives. The observations were commenced before institution of therapy, and were continued until all clinical evidence of the deficiency had disappeared. The patients had been on diets low in nicotinic acid for appreciable periods, and all of them presented one or more of the manifestations of nicotinic acid deficiency (glossitis, stomatitis, scaling dermatitis, diarrhea, etc.) at the time of admission to the hospital. Five of them suffered, in addition, from anorexia incident to coexisting disease (stricture of the common bile duct, subphrenic abscess following perforation of the gall-bladder, unresolved pneumonia with multiple abscess formation, toxic adenoma of the thyroid, and chronic bronchitis and emphysema.) There was no significant coexisting disease in the remaining three patients, although one suffered from chronic alcoholism. There were five males and three females in the group, and their ages ranged from 51 to 81 years. Two additional 24 hour collections of urine,* one specimen from each of two patients suffering from endemic pellagra, were also examined in this same manner. The porphyrin content of a four day collection of feces from each of these patients was also determined.*

Urines from seven patients receiving deep roentgen therapy for carcinoma of the cervix uteri were examined in a similar manner.† This portion of the study was undertaken because of a report that irradiation sickness was often associated with a positive Beckh-Ellinger-Spies test.[15] The observations were started prior to the institution of the deep roentgen therapy, and were continued during the course of treatment. These women, whose ages ranged from 31 to 65 years, were in the hospital during the entire period of observation. None of them exhibited any clinical evidence of nicotinic acid deficiency. Except when nausea occurred, there was no interference with appetite, and they received the standard hospital diet. No vitamin preparations were given them during this period. The patients were closely

---

* Study of the urine and feces from these two patients was made possible through the courtesy of Dr. David Smith, Duke University, Durham, N. C.
† We are grateful to Dr. John L. McKelvey, Department of Obstetrics and Gynecology, and to Dr. K. W. Stenstrom, Department of Roentgen Therapy, for their coöperation in this study.

observed for development of nausea and vomiting.   When this occurred, no specific measures were instituted other than the intravenous administration of 5 per cent glucose in physiological saline when the nausea was severe, or when accompanied by emesis.

The third group of patients consisted of 38 unselected consecutive cases of arthritis as they appeared at the Out-Patient Department.   This group was studied because of a report by Lutterloh [16] that the B.E.S. test was commonly positive in cases of arthritis.   All of the patients were questioned and examined for symptoms or signs of nicotinic acid deficiency; no evidence of such was present in any.   Except for a few instances, the patients had no complaints except those referable to the arthritis.   In seven the arthritis was of the atrophic or rheumatoid type; in 30 it was of the hypertrophic variety, and in one it was due to gonorrhea.   A single specimen of urine was obtained from each of these patients, and was examined immediately after voiding.

The fourth group consisted of five patients who were admitted to the hospital in severe diabetic acidosis.   Spies and co-workers [17] noted frequent positive B.E.S. tests in diabetic acidosis and suggested a correlation with what they believed to be a reduction of codehydrogenase in the blood.   One or more specimens of urine were examined (immediately after passage) from each of these patients.   None of the patients exhibited any clinical evidence of nicotinic acid deficiency.

The final group consisted of 16 normal individuals.   One or more specimens of urine were examined (immediately after voiding) from each of these subjects.

The following procedures were used:

1. Ellinger-Dojmi or Beckh-Ellinger-Spies (B.E.S.) test.   This test was carried out in the exact manner described by these authors.[4]   A constant amount of urine (10 c.c.) was used in all the determinations.

2. B.E.S. test plus nitrite.   One or two drops of a 2 per cent solution of KNO_2 were added to 10 c.c. of urine, and the B.E.S. test was then carried out in the usual manner.

3. Nencki-Sieber (N.S.) test.[18]   Ten cubic centimeters of urine were strongly acidified with 5 c.c. of 25 per cent HCl, and then extracted with 2 c.c. of primary normal amyl alcohol.

4. N.S. test plus nitrite.   One or two drops of a 2 per cent solution of KNO_2 were added to 10 c.c. of urine, and the N.S. test was then carried out in the above manner.

It will be noted that the same amounts of urine were used in each of the four tests, so that the intensities of the reactions were comparable.   Furthermore, the 25 per cent HCl in the B.E.S. tests and the amyl alcohol in the N.S. tests were examined spectroscopically in order to exclude the possibility that the red color was due to substances other than urorosein.

5. Obermayer's test for indican.   Equal parts of urine and Obermayer's reagent were mixed in a test tube, and the indican was then extracted with a small amount of chloroform.

6. Starch-iodine test for nitrite.   Six to eight cubic centimeters of urine were acidified with a few cubic centimeters of 2 N H_2SO_4.   Three to four cubic centimeters of 5 per cent solution of potassium iodide and a few cubic centimeters of a freshly prepared solution of 1 per cent starch were then added.   We have found this test sensitive for concentrations of KNO_2 as low as 0.0004 gram per 100 c.c.

7. Quantitative determinations of urinary porphyrin were made on the two 24 hour collections of urine from the two patients suffering from endemic pellagra.   In the other instances, porphyrin was removed from the acetic acid-ether extract of the urine (in the B.E.S. test) by preliminary extraction with 5 per cent HCl.   As was pointed out in a previous report,[2] this extraction with 5 per cent HCl serves to distinguish whether the color reaction in the B.E.S. test is due to porphyrin (removed quantitatively in the 5 per cent HCl) or to urorosein (removed from the acetic-ether extract of urine by the 25 per cent HCl).   Coproporphyrin was determined in the 24 hour urines and the four day collections of feces from the two cases of endemic pellagra by means of the following modification of the Fikentscher method.[19]

Urine: 100 c.c. were placed in a separatory funnel and strongly acidified with glacial acetic acid.   Three extractions with 30 c.c. portions of ether were then carried out.   The combined ether was washed twice with small amounts of water and extracted four times with 2 to 3 c.c. portions of 5 per cent HCl.   The combined 5 per cent HCl solution was extracted twice with chloroform, after which it was made negative (red) to Congo paper by addition of saturated solution of sodium acetate.   The solution was then extracted three times with ether.   The combined ether after being washed twice with small amounts of water was extracted four times with 2 c.c. portions of 1 per cent HCl.   The amount of coproporphyrin in this final solution was determined by fluorimetry in the usual way,[20] a Zeiss stufenphotometer and a standard coproporphyrin solution being employed.

Feces: 10 gm. of the mixed four day collection of feces were ground thoroughly in a mortar with glacial acetic acid and the mixture was then extracted six times with ether.   Further small amounts of glacial acetic were added after every other extraction with ether.   The acetic and ether extract was poured off in each instance and filtered into a separatory funnel.   The combined extract was washed twice with small amounts of water, then extracted repeatedly with 5 per cent HCl.   This was continued until the extract no longer exhibited any appreciable red fluorescence in ultraviolet light (carbon arc fitted with Corning red purple ultra filter).   The 5 per cent HCl was then made negative to Congo paper by addition of a saturated sodium acetate solution, and three extractions with ether were carried out.   The ether was washed twice with water and was then extracted five to seven times with 2 c.c.

portions of 1 per cent HCl (the number of extractions being determined by the removal of red fluorescence). The combined 1 per cent HCl was washed twice with ether which was added to the ether which had just been extracted. This removes small amounts of protoporphyrin which were entrained during the extraction with 1 per cent HCl. The combined ether was then extracted five times with 2 c.c. portions of 5 per cent HCl. This constituted the final protoporphyrin fraction. The 1 per cent HCl fraction was then diluted to 0.2 per cent and extracted repeatedly with chloroform, again determining the number of extractions by means of the red fluorescence. After dilution of the chloroform with four volumes of ether any porphyrin contained was removed by repeated extraction with 1 per cent HCl. This constituted the final "deutero" fraction which includes both deutero and pseudodeuteroporphyrins.[21] The 0.2 per cent HCl remaining after the above chloroform extraction was made negative to Congo paper by addition of sodium acetate solution, after which it was extracted three times with ether. The latter was washed in the usual way and was then extracted four or more times, depending on fluorescence, with 2 c.c. portions of 1 per cent HCl. This was the final coproporphyrin solution. The red fluorescence of the proto-, deutero-, and coproporphyrin fractions was then measured in the usual way by comparison with a standard coproporphyrin solution in 1 per cent HCl, in the stufenphotometer.[20]

8. Toluene was added to a portion of each 24 hour specimen of urine. This portion was then set aside for a period of at least three weeks, and observed for the development of a red color in the toluene layer. During this period the B.E.S. and indican tests were repeated in many of the urines, especially if the toluene became pink or red. All of the toluene preservatives which became pink or red were eventually pooled and were concentrated in vacuo to a very small volume. The various pigments present were then separated by chromatographic analysis. The results of this part of the study will be described separately.

RESULTS

Patients Having Nicotinic Acid Deficiency. Positive spontaneous urorosein reactions (without addition of nitrite) in urines examined immediately after voiding have been noted at one time or another in each of the eight cases of nicotinic acid deficiency. The spontaneous urorosein reaction was often positive during the period of relapse, but it was often noted to disappear prior to the administration of nicotinic acid, and to reappear (even in specimens examined immediately after voiding) long after adequate amounts of nicotinic acid had caused regression of all signs of deficiency (table 1).

Following the addition of nitrite, the urorosein reaction was observed in all but three of 224 urines examined from the eight patients having a deficiency of nicotinic acid (table 2). It did not appear that the amount of the chromogen of urorosein excreted daily in the urine was influenced by the

TABLE I

Summary of Data from Patient Having Alcoholic Pellagra, Showing Absence of Correlation Between B.E.S. Test and Clinical Evidence of Nicotinic Acid Deficiency.*

Dates	B.E.S.	B.E.S. plus KNO₂	N.S.	N.S. plus KNO₂	Ober-mayer	Nitrite	Toluene (observed for three weeks)	Diet	Nicotinic Acid mg. (daily)		Remarks
									I.V.	Orally	
6–15 to 6–21	Neg.	+	Neg.	+	Neg. or +	Neg.	Clear	Low vitamin B	—	—	Tongue red and atrophic. Symmetrical brown scaling pigmentation of both hands and wrists.
6–22 to 6–30	Neg.	+	Neg.	+	Neg. or +	Neg.	Clear	Low vitamin B	100	300	
7–1 to 7–17	Neg.	+	Neg.	+	Neg. or +	Neg.	Clear	High vitamin 3000 calories	100	300	7–17: All clinical evidence of pellagra has disappeared.
7–18	+	+	+	+	Neg.	Neg.	Clear	High vitamin 3000 calories	100	300	
7–19	+	+	+	+	+	+	Clear	High vitamin 3000 calories	100	300	
7–20 to 7–21	Neg.	+	Neg.	+	+	Neg.	Clear	High vitamin 3000 calories	100	300	7–21: Patient discharged. No clinical evidence of pellagra.

* Study of this patient was made possible through the coöperation of Dr. George E. Fahr of the Minneapolis General Hospital.

administration of nicotinic acid. No quantitative measurements were made, but since all the tests were performed using the same amount of urine and reagents, the intensities of the reactions were comparable. The administration of thiamin, and in one instance, of riboflavin, did not influence the presence or the intensity of the reaction.

Herter [22] demonstrated that the urorosein reaction of Nencki and Sieber was produced by the oxidation of indolacetic acid, and it is probable that indolacetic acid is the chromogen of the red pigment which develops in the 25 per cent HCl in the B.E.S. test.[2] Correspondingly, the results of the B.E.S. and N.S. tests in the 224 urines from the eight patients with nicotinic acid deficiency were in agreement in all instances.

In order to identify the urorosein reaction with greater certainty, the 25 per cent HCl in the B.E.S test and the amyl alcohol in the N.S. test were

TABLE II

Summary of the Results of the Tests for Urinary Pigments in the Five Groups of Patients Examined.

Type of Case	Number of Patients	Total Number of Determinations	Test Positive Without Addition of Nitrite		Test Positive Only Following Addition of Nitrite		Test Negative Following Addition of Nitrite		Urinary Indican		Starch-Iodine Test Positive for Nitrite	Development of Red Color in Toluene Preservative
			B.E.S.	N.S.	B.E.S.	N.S.	B.E.S.	N.S.	Neg. or +	++ to ++++		
Nicotinic acid deficiency	8	224	72	72	149	149	3	3	175	49	42	72
Squamous cell carcinoma of cervix uteri, receiving deep roentgen therapy	7	173	10	10	28	28	135	135	169	4	14	60
Arthritis	38	38	1	1	35	35	2	2	32	6	0	0
Diabetic acidosis	5	8	0	0	7	7	1	1	8	0	0	0
Normals	16	34	0	0	19	19	15	15	30	4	0	0

examined spectroscopically on repeated occasions in each case. The absorption of urorosein in 25 per cent HCl (B.E.S. test) is characterized by a relatively weak, broad, diffuse band, having its maximum absorption at 543 to 544 mμ. A second weaker band is present at 511 mμ. In every urine in which the B.E.S. test was positive, either spontaneously or following the addition of nitrite, this characteristic absorption was present. The addition of nitrite to urine which gave a positive test spontaneously did not alter the spectroscopic absorption. When urorosein is concentrated in amyl alcohol in the N.S. test, it exhibits a similar absorption with a maximum at 543 to 544 mμ, although in some instances the absorption was shifted toward the red, the maximum varying from 546 to 553 mμ. The addition of nitrite to urines in which the N.S. test was spontaneously positive usually did not significantly alter the absorption spectra. In a few, however, the maximum intensity of the band was displaced after addition of nitrite, and in almost all such instances, the displacement was slightly toward the red end of the spectrum.

Urinary Nitrite. Of the 224 urines from the eight patients with nicotinic acid deficiency, the starch-iodine test was positive in 42, indicating the presence of nitrite or of a similar oxidizing agent. It is significant that in each of these 42 urines the B.E.S. and N.S. tests were also spontaneously positive. The addition of nitrite to the urine in the amount described did not influence

these tests except in one instance. In this case the B.E.S. test was unchanged but the color of the amyl alcohol in the N.S. test rapidly became yellow. This may have indicated simply an over-oxidation, since Homer [23] has reported that the color of various indol derivatives is transformed to yellow or brown in the presence of an excess of oxidizing agent. In 30 urines, the starch-iodine test was negative, but the B.E.S. and N.S. tests were spontaneously positive. It would appear that these urines contained an oxidizing agent other than nitrite, since the starch-iodine test is sensitive for smaller concentrations of nitrite than are required to give a positive urorosein reaction with pure indolacetic acid. The oxidizing substances, other than nitrite, which are present in the freshly voided urine, and which are responsible for the spontaneous B.E.S. and N.S. tests have not been identified. None of the patients had infections or other lesions in the urinary tract which might be responsible for the production of such substances.

Urinary Indirubin-Like Substances. The toluene preservatives of pellagra urines, also of urines from certain other patients suffering from malnutrition of one cause or another, often develop a pink or even deep red color.[1, 2] In many instances the red color is due to the formation of an indirubin-like substance.[1, 2] The present investigation has sought to determine whether the occurrence of this substance was in any way correlated with the presence of indolacetic acid, indican, the presence of an oxidizing agent in the urine, or a combination of these substances.

A pink or red color developed in the toluene in 72 of the 224 urines from the eight cases with nicotinic acid deficiency. In the remaining 152, the toluene remained clear. The B.E.S. and N.S. tests were also positive without the addition of an oxidizing agent in 72 urines but not necessarily the same samples. In 25 of these, the toluene became red; it remained clear in the other 47. In the urines in which the B.E.S. and N.S. tests were positive only after addition of nitrite, the toluene became red in 45 and remained clear in 104. The presence of nitrite or similar oxidizing substance in the urine does not, therefore, appear to be necessary to the formation of this red pigment.

When the toluene preservatives of these urines were subjected to chromatographic analysis, several pigments were found to be present. These included a red crystalline substance, closely related at least to indirubin. The general behavior of the red toluene-soluble pigments from both human and dog urine have been studied and their absorption in ultra-violet light compared with that of crystalline indirubin. These observations will be presented in a subsequent report.

In 49 of the 224 specimens of urine, the indican reaction was greater than 1 (graded on a basis of 4). In 31 of these the toluene became red; in the other 18 the toluene remained clear. There were 175 urines in which the indican reaction was less than one. In 134 of these the toluene remained clear, whereas in 41 a red pigment appeared. These observations suggest

that the formation of these red pigments occurs more frequently in those urines which contain a larger amount of indican, than in those in which the amount of indican is normal. On the other hand, a red color developed in the toluene of five urines in which the Obermayer reaction was consistently negative, as well as in several others in which the reaction was very weak. The possibility exists, however, that given the proper conditions indolacetic acid and indoxyl may unite to form indirubin. In 11 instances, we have observed that the toluene layer became red coincidentally with the disappearance of the urorosein reaction, and frequently, with a diminution in the intensity of the indican reaction. Again, however, a red color developed in the toluene in 13 urine samples in which there was no apparent change in the intensity of the urorosein reaction. Inasmuch as quantitative estimations of indolacetic acid were not made, it is quite possible that only a part was utilized in these instances in the formation of indirubin.

Urinary Indican. In seven of the eight patients with nicotinic acid deficiency, the amounts of indican in the urine were within normal limits prior to treatment and were not influenced by the administration of nicotinic acid. The remaining patient had a marked increase of indican in the urine, and this decreased following treatment. The decrease in urinary indican in this patient may have been due to the effect of thiamin (which was administered over the same period as the nicotinic acid) upon the size and motility of the large bowel, since considerable improvement in the function of the colon occurred following institution of therapy.

Urinary Porphyrin. In none of the patients with nicotinic acid deficiency whom we have studied was the amount of porphyrin in the urine sufficient to be productive of color with the Ellinger-Dojmi reaction. This fact was readily ascertained by preliminary removal of porphyrin from the ether extract of the urine with 5 per cent HCl. The urorosein reaction was then developed by extraction from the ether with 25 per cent HCl, according to the Ellinger-Dojmi procedure. In every urine so examined, preliminary removal of porphyrin with 5 per cent HCl did not interfere with the intensity of the color reaction produced by urorosein in the 25 per cent HCl. Since quantitative studies of urinary porphyrin excretion were not performed in the eight cases of nicotinic acid deficiency which we studied, the fact remains that slightly increased amounts of coproporphyrin may have been present. In the two 24 hour collections of urine from two patients suffering from endemic pellagra which were sent to us from Duke University, there were 57.8 and 75.8 micrograms of coproporphyrin, respectively. These values are within normal limits. The B.E.S. test was strongly positive in both instances. By way of comparison it may be noted that the urine from a typical case of lead colic contained 720 γ in 24 hours, a tenfold increase, yet the B.E.S. test was negative. (The volume of urine was 1900 c.c.) Spectroscopic examination of the 25 per cent HCl from the B.E.S. test in this instance revealed weak porphyrin absorption, although the solution was prac-

tically colorless. This again reveals the complete independence of the B.E.S. test with respect to porphyrinuria. We believe that the test would not be significantly positive due to porphyrin except possibly in certain cases of idiopathic porphyria in which relatively large amounts of coproporphyrin are excreted. In most of these cases, the excess porphyrin is, of course, uroporphyrin, which is insoluble in ether, and could not, therefore, contribute to the B.E.S. test. The latter has been negative in the urines of five cases of idiopathic porphyria observed by us.

Since it has been suggested that the light sensitivity in pellagra is due to porphyrin [8] the possibility existed that there might be increased porphyrin in the feces even if not in the urine. H. van den Bergh has observed a case of idiopathic porphyria with light sensitivity, but without porphyrinuria.[41] At the suggestion of Dr. David Smith of Duke University Medical School, the stool specimens from two of his cases of endemic pellagra were studied quantitatively as described in the foregoing. The results were as follows:

1. Wt. of 4 day feces = 479 gm.

	γ per day
Protoporphyrin	3,280
Deuteroporphyrin	750
Coproporphyrin	400

2. Wt. of 4 day feces = 500 gm.

	γ per day
Protoporphyrin	1000
Deuteroporphyrin	1000
Coproporphyrin	242

The values for coproporphyrin are within normal limits, while the values for proto- and deuteroporphyrin (which are, of course, only relative) are considerably increased. This increase, however, is readily explained by the presence of occult blood in both samples (positive hemochromogen reaction).

Results in Patients Receiving Deep Roentgen Therapy. One hundred and seventy-three specimens of urine were examined from seven patients receiving deep roentgen therapy for squamous cell carcinoma of the cervix uteri. The results of this study are shown in table 2. A positive starch-iodine test for nitrite occurred in seven urines in which the precursor of the urorosein reaction was absent, with the result that the B.E.S. and N.S. tests were negative in these instances. This group of cases differs from the preceding in that the majority of the urines (78 per cent) failed to develop a positive urorosein reaction even after the addition of KNO_2. In no instance was the amount of porphyrin in the urine of these cases sufficient to be productive of color with the Ellinger-Dojmi reaction.

The occurrence of nausea, or nausea and vomiting could not be correlated either with the presence of positive B.E.S. or N.S. tests, with the amount of indican in the urine, or with the presence of an oxidizing agent in the urine. In three instances, spontaneous positive B.E.S. and N.S. tests

occurred prior to the start of the deep roentgen therapy. In one patient nausea occurred eight times during the 33 days of observation. The B.E.S. and N.S. tests were positive on only two occasions during this same period.

In 60 of these urines the toluene preservatives became pink or red when the urine was allowed to stand. In 33 of these 60 the urorosein reaction had been negative even after the addition of nitrite and there were only traces of indican present.

Results in Patients Suffering from Arthritis. In only one of the 38 urines examined from this group of patients was the urorosein reaction positive without the addition of nitrite. In two of the specimens there was insufficient chromogen present to give a positive test even after the addition of nitrite. As a group, the amounts of indican in these urines were not increased (see table 2), and in none did the toluene preservative become pink or red.

Results in Patients with Diabetic Acidosis. Eight specimens of urine were examined from five patients admitted to the hospital in severe diabetic acidosis. The urorosein reaction was not spontaneously positive in any, but was positive in seven following the addition of nitrite (table 2). A red color failed to develop in the toluene preservative of any of the eight urines.

Results in Normal Individuals. Thirty-four specimens of urine were obtained from 16 normal subjects and were examined immediately after voiding. The urorosein reaction was not positive spontaneously in any of these, but in 19 it became positive after the addition of nitrite (table 2). A red color failed to develop in the toluene of any of the 34 urines. Urinary indican was increased in four of the 34 samples. In none of the 34 was the starch-iodine test positive for nitrite.

DISCUSSION

The red pigment developing in certain urines after the addition of a strong mineral acid was named urorosein by Nencki and Sieber.[18] The chromogen of this reaction was identified by Herter as indolacetic acid.[22] Herter [24] also pointed out that the presence of an oxidizing agent in the urine was essential to the development of the reaction.

A varying incidence of positive urorosein reactions in normal and pathological urines has been reported by different investigators. Nencki and Sieber [18] noted positive tests in 10 per cent of all pathological urines, and negative tests in the urine from all normal subjects. A positive test occurred in every normal urine examined by Rosin [25] although in some the test was faint. Garrod and Hopkins [26] stated that the chromogen of urorosein is a common constituent of pathological urines, and that it is sometimes present in traces in normal urines. Herter [22] reported the urorosein reaction to be very faint in the urine of normal subjects, but that the reaction was increased following the consumption of large quantities of meat. Ross [27] found that the urines of 21 per cent of 93 healthy individuals and 43 per cent of 490

insane individuals gave a positive test following the addition of sodium nitrite. Without the aid of an oxidizing agent the tests were positive in 7.7 and 11 per cent of the cases, respectively. Gross, Sasaki, and Spies [28] report the presence of a positive (B.E.S.) test in the urine of 13 of 45 medical students. The widely divergent nature of the above reports is due probably to differences in the technic used by the various investigators (use of an oxidizing agent, amount and concentration of urine and acid, the presence of other pigments in the urine soluble in amyl alcohol which mask the color, etc.).

The development of a red color in the 25 per cent HCl in the Beckh-Ellinger-Spies test is obviously dependent upon two substances, the chromogen of urorosein, and an oxidizing agent. Since the chromogen is present in a high percentage of urines (normal as well as pathological), the chief variable in this reaction is the oxidizing agent. Herter [24] noted that nitrites were formed in many urines on standing, through the action of nitrifying bacteria. Meiklejohn and Kark [13] observed that oxidizing substances developed in urines on standing, even when kept sterile. Ross [27] obtained positive urorosein reactions in specimens of urine examined immediately after they were passed, and similar results have been obtained by Meiklejohn and Kark, [13] and by us.

Since this oxidizing agent (as yet unidentified) may occur in the freshly voided urine of normal persons, or long after all evidence of pellagra has disappeared (table 1), its presence in the urine cannot be considered as a specific test for nicotinic acid deficiency. It does appear from our studies, however, that the spontaneous urorosein reaction occurs much more frequently and in greater intensity in individuals suffering from nicotinic acid deficiency than in normal subjects.

An alteration in the mode of putrefaction of tryptophane associated with changes in the flora of the intestinal bacteria may be a contributing factor in the production of the urorosein reaction. Hopkins and Cole [29] have shown that tryptophane yields indolacetic acid when acted upon by anaerobic bacteria, whereas under aerobic conditions of growth, skatolcarbonic acid, skatol, and indol are formed. This difference in the metabolism of tryptophane may account, at least in part, for the observations that a reciprocal ratio exists between the output of indican and of urorosein in the urine, and that this ratio may be influenced by diet. [14, 25, 30] Decarboxylation of the amino acids may be effected by a large number of organisms, especially anaerobic bacilli. The action of such bacteria on tryptophane, therefore, may lead to the production of indolethylamine. When this substance was perfused through the surviving liver of the rabbit or cat, Ewins and Laidlow [31] found the perfusion fluid gave a strong urorosein reaction, and that indolacetic acid could be isolated from this fluid. It has not been demonstrated that an altered tryptophane metabolism is responsible for the urorosein reaction in human urine, but since many of the conditions in which a

strong urorosein reaction have been reported are accompanied by some degree of intestinal disorder, this point requires further study.

Increased urinary excretion of coproporphyrin has been observed in alcoholic pellagra by Dobriner, Strain, and Localio,[32] and by Watson.[1]   Following treatment with yeast and nicotinic acid, a significant decrease in the amounts occurred.   Rosenblum and Jolliffe [33] reported an increased urinary excretion of porphyrin in six of nine inebriates who had either a pellagrous stomatitis, dermatitis, or both.   In three of the subjects there appeared to be a definite correlation between the severity of the pellagra and porphyrin excretion.   More recently, Kark and Meiklejohn [44] have reported no increase of urinary porphyrin in six of seven cases of pellagra; a slight increase was observed in one instance of alcoholic pellagra.   No correlation exists between the B.E.S. test and the actual amounts of urinary porphyrin, as shown by Watson,[1] and Dobriner and Rhoads.[12]   Furthermore, in none of the patients suffering from nicotinic acid deficiency whom we have studied was the amount of porphyrin in the urine sufficient to be productive of color in the Ellinger-Dojmi reaction.   The amounts of porphyrin present in the urine in alcoholic pellagra are not as great as are often encountered in lead poisoning, cirrhosis of the liver, or other pathological states.   There is, therefore, no reason to suppose, as has been suggested, that the light sensitivity in pellagra is related to porphyrin.   The amounts in the urine and feces of the two cases of endemic pellagra of the present study were normal.

An increased excretion of coproporphyrin in the feces has been noted in one case of pellagra associated with chronic alcoholism by Dobriner, Strain and Localio.[32]   An average of 643 micrograms of coproporphyrin was excreted daily in the feces by this patient during a six-day control period. Following nine days of treatment with yeast extract and the intramuscular injection of liver extract, the fecal excretion of coproporphyrin decreased to less than half of the original level.   Large amounts of protoporphyrin and deuteroporphyrin were also found in the feces of this patient, but these may well have been the result of bleeding into the gastrointestinal tract, as these authors have suggested.   It may be noted that blood loss alone is sufficient to increase erythropoiesis and with this, the amount of coproporphyrin in the feces.[34]

The B.E.S. test has also been used as a measure of porphyrin excretion in roentgen sickness.   Spies, Bean, and Stone [35] reported "abnormally large" amounts of porphyrin in the urine of seven cases of radiation sickness, and stated that these levels returned to normal following the administration of nicotinic acid.   Graham [15] reported that 10 of 52 patients suffering from radiation sickness "showed a material increase in porphyrinuria," using the method of Beckh, Ellinger, and Spies.[4]   He stated that all but one of these returned to normal after the administration of nicotinic acid, and that "even when the excretion of porphyrin appeared to be within normal limits in most cases, it was decreased when nicotinic acid was given."

In none of seven patients receiving deep roentgen therapy in our series was the amount of porphyrin present in the urine sufficient to be productive of color when extracted from the ether extract (in the B.E.S. procedure) with 5 per cent HCl. We were unable to establish any correlation between a positive B.E.S. test and the occurrence of nausea in these patients. Furthermore, in every instance the B.E.S. test became negative within one or two days without the administration of nicotinic acid.

Lutterloh [16] has reported the B.E.S. test to be positive in 14 of a group of 49 patients suffering from atrophic arthritis. In our study of 38 unselected arthritics having no clinical evidence of nicotinic acid deficiency, we found only one positive B.E.S. test (in a patient with hypertrophic arthritis).

Vilter, Vilter, and Spies [17] noted the B.E.S. test to be positive in one of two cases of severe diabetic acidosis, and reported that this test became negative following treatment of the acidosis. In five cases which we have observed, we have found the test to be negative. Although codehydrogenase I was believed by these investigators to be deficient in the blood of pellagrins in relapse as well as in the blood of diabetics in severe acidosis, there is insufficient evidence that lack of this substance is responsible for the conditions which lead to the production of a positive B.E.S. test.

A strongly positive indican reaction has been described in the urine of patients suffering from endemic pellagra,[14, 36, 37, 38] and it has been noted frequently that the indicanuria decreases as the patient recovers. On the other hand, the production of pellagra in 11 human volunteers by Goldberger and Wheeler [39] was not accompanied by marked indicanuria. In these 11 subjects the indican reaction of the urine was recorded as negative more often than positive. The incidence of indicanuria appears to be greater among cases with a deficiency of gastric acid,[14, 40] and it has been suggested that the diminished gastric acidity is indicative of the strong inhibitory influence of the normally acid gastric juice upon gastrointestinal putrefaction. In only one of our eight cases was the amount of indican in the urine significantly increased. Since both thiamin and nicotinic acid were administered simultaneously to this patient, it is not possible to state with certainty that nicotinic acid was responsible for the decreasing indicanuria which accompanied his clinical improvement. In the remaining seven patients the amounts of indican in the urine were within normal limits prior to treatment, and were not significantly altered by the administration of nicotinic acid.

Since completion of the studies described above, Najjar and Holt [42] have described a specific urinary reaction which is apparently dependent upon the store of nicotinic acid in the body. The substance responsible for this reaction has not been identified, but the bluish fluorescence which it produces in ultraviolet light may be measured quantitatively. After the ingestion of nicotinic acid the excretion of this substance increased. It was demonstrated that the substance responsible for the fluorescence disappears from

the urine of patients with pellagra and of dogs with blacktongue.[43]   A second unknown substance which produces fluorescence in the "blank," has been observed to be increased in pellagra.

When an aqueous solution of indolacetic acid, or of indolacetic acid plus a few drops of 2 per cent KNO_2, was used in this test, no increased fluorescence occurred.   After shaking with 'permutit, the solution of indolacetic acid was decanted and tested for the urorosein reaction.   The urorosein reaction which resulted was as intense as occurred with a similar control solution, indicating that neither indolacetic acid nor an intermediate compound in the urorosein reaction was adsorbed on the permutit.   It appears from these observations, therefore, that no direct relationship exists between the substances which are responsible for the fluorescence reaction of Najjar and Holt and the urorosein test in pellagra.

CONCLUSIONS

1. The chromogen of the urorosein reaction is a normal constituent of the urine of many individuals who have no clinical evidence of nicotinic acid deficiency.   The available evidence indicates that this chromogen is indolacetic acid.

2. The development of the urorosein reaction either by the method of Nencki and Sieber, or that of Beckh, Ellinger and Spies, requires the presence of nitrite or a similar oxidizing agent.   Substances of this type are native to urines which exhibit spontaneous reactions.   The exact nature of these native substances remains to be determined.

3. No definite correlation has been noted between the presence and disappearance of either chromogen or oxidizing agent, with the deficiency or administration respectively, of nicotinic acid.   The results of the present investigation indicate, however, that spontaneous reactions (without addition of nitrite) occur only in association with disease and much more frequently in subjects having deficiency states.

4. The Ellinger-Dojmi color reaction, on which the B.E.S. test is based, is not at all specific for porphyrin, and in our experience has always been due to urorosein.

5. The development of a red color in the toluene preservatives of pellagra urines, also of urines from certain patients with malnutrition of one cause or another, could not be correlated with other evidence of nicotinic acid deficiency.   This pigment has not been observed to develop in urines of normal individuals.

BIBLIOGRAPHY

1. WATSON, C. J.: The urinary pigments in four cases of alcoholic pellagra, Proc. Soc. Exper. Biol. and Med., 1938, xxxix, 514–518.
2. WATSON, C. J.: Further observations on the red pigments of pellagra urines, Proc. Soc. Exper. Biol. and Med., 1939, xli, 591–595.

3. ELLINGER, P., and DOJMI, L.: Note on the presence of porphyrine in the urine of pellagra patients, Chemistry and Industry, 1935, liv, 507.

4. BECKH, W., ELLINGER, P., and SPIES, T. D.: Porphyrinuria in pellagra, Quart. Jr. Med., 1937, vi, 305–319.

5. SYDENSTRICKER, V. P., SCHMIDT, H. L., JR., FULTON, M. C., NEW, J. S., and GEESLIN, L. E.: Treatment of pellagra with nicotinic acid: Observations in 45 cases, South. Med. Jr. 1938, xxxi, 1155–1163.

6. SPIES, T. D., COOPER, C., and BLANKENHORN, M. A.: The use of nicotinic acid in the treatment of pellagra, Jr. Am. Med. Assoc., 1938, cx, 622–627.

7. SPIES, T. D., GROSS, E. S., and SASAKI, Y.: Effect of yeast and nicotinic acid on porphyrinuria, Proc. Soc. Exper. Biol. and Med., 1938, xxxviii, 178–181.

8. SPIES, T. D., SASAKI, Y., and GROSS, E. S.: A note on the relationship of porphyrinuria to human pellagra, South. Med. Jr., 1938, xxxi, 483–486.

9. SPIES, T. D., ARING, C. D., GELPERIN, J., and BEAN, W. B.: The mental symptoms of pellagra. Their relief with nicotinic acid, Am. Jr. Med. Sci., 1938, cxcvi, 461–475.

10. SPIES, T. D., GRANT, J. M., STONE, R. E., and McLESTER, J. B.: Recent observations on the treatment of six hundred pellagrins with special emphasis on the use of nicotinic acid in prophylaxis, South. Med. Jr., 1938, xxxi, 1231–1237.

11. SPIES, T. D., VILTER, R. W., and ASHE, W. F.: Pellagra, beriberi, and riboflavin deficiency in human subjects, Jr. Am. Med. Assoc., 1939, cxiii, 931–937.

12. DOBRINER, K., and RHOADS, C. P.: Quantitative determination of urinary coproporphyrin, New England Jr. Med., 1938, ccxix, 1027–1029.

13. MEIKLEJOHN, A. P., and KARK, R.: Pigment excretion in pellagra, New England Jr. Med., 1939, ccxxi, 519–521.

14. HUNTER, A., GIVENS, M. H., and LEWIS, R. C.: Preliminary observations on metabolism in pellagra, Hygienic Laboratory Bulletin No. 102, pp. 39–68, (Feb.) 1916.

15. GRAHAM, J. W.: Radiation sickness. Treatment with nicotinic acid, Jr. Am. Med. Assoc., 1939, cxiii, 664–667.

16. LUTTERLOH, C. H.: Discussion of paper by Dr. Seale Harris: The genesis of pellagra, South. Med. Jr., 1940, xxxiii, 1044–1056.

17. VILTER, R. W., VILTER, S. P., and SPIES, T. D.: Determination of the codehydrogenases I and II (cozymase) in the blood of diabetics in severe acidosis, Am. Jr. Med. Sci., 1939, cxcvii, 322–326.

18. NENCKI, M., and SIEBER, N.: Ueber das Urorosein, einen neuen Harnfarbstoff, Jr. f. prakt. Chem., 1882, xxvi, 333–336.

19. FIKENTSCHER, R.: Quantitative Porphyrin—Bestimmung durch Lumineszenzintensitäts—messung mit dem Stufenphotometer, Biochem. Ztschr., 1932, ccxlix, 257–269.

20. WATSON, C. J., PASS, I. J., and SCHWARTZ, S.: A study of the supposed conversion of protoporphyrin to coproporphyrin by the liver. I. The fate of parenterally administered protoporphyrin in dogs with bile renal fistulae, Jr. Biol. Chem., 1941, cxxxix, 583.

21. WATSON, C. J.: Concerning the naturally occurring porphyrins. V. Porphyrins of the feces, Jr. Clin. Invest., 1937, xvi, 383–395.

22. HERTER, C. A.: On indolacetic acid as the chromogen of the "Urorosein" of the urine, Jr. Biol. Chem., 1908, iv, 253–257.

23. HOMER, A.: A spectroscopic examination of the color reactions of certain indol derivatives and of the urine of dogs after their administration, Jr. Biol. Chem., 1915, xxii, 345–368.

24. HERTER, C. A.: The relation of nitrifying bacteria to the urorosein reaction of Nencki and Sieber, Jr. Biol. Chem., 1908, iv, 239–251.

25. ROSIN, H.: Ein Beitrag zur Lehre von den Harnfarbstoffen. (Ueber das sogenannte Urorosein, Harnrosa), Deutsch. med. Wchnschr., 1893, xix, 51–54.

26. GARROD, A. E., and HOPKINS, F. G.: On urobilin. I. The unity of urobilin, Jr. Physiol., 1896, xx, 112–114.

27. Ross, E. L.: A preliminary note on the excretion of indolacetic acid in the urine, Arch. Int. Med., 1913, xii, 112–116.

28. Gross, E. S., Sasaki, Y., and Spies, T. D.: Effects of nicotinic acid on increased porphyrinuria occurring in seven painters, Proc. Soc. Exper. Biol. and Med., 1938, xxxviii, 289–292.

29. Hopkins, F. G., and Cole, S. W.: A contribution to the chemistry of proteids. Part II. The constitution of tryptophane and the action of bacteria upon it, Jr. Physiol., 1903, xxix, 451–466.

30. Dean, J. A.: Urorosein, Jr. Am. Pharm. Assoc., 1920, ix, 252.

31. Ewins, A. J., and Laidlow, P. P.: The fate of indolethylamine in the organism, Biochem. Jr., 1913, vii, 18–25.

32. Dobriner, K., Strain, W. H., and Localio, S. A.: Excretion of porphyrin in pellagra, Proc. Soc. Exper. Biol. and Med., 1938, xxxviii, 748–752.

33. Rosenblum, L. A., and Jolliffe, N.: Porphyrinuria in pellagra, Am. Jr. Med. Sci., 1940, cxcix, 853–858.

34. Dobriner, K., and Rhoads, C. P.: The excretion of coproporphyrin I following hemorrhage in dogs, Jr. Clin. Invest., 1938, xvii, 105–108.

35. Spies, T. D., Bean, W. B., and Stone, R. E.: The treatment of subclinical and classic pellagra, Jr. Am. Med. Assoc., 1938, cxi, 584–592.

36. Billings, F., Green, J. L., Ormsby, O. S., Webster, G. W., Grindley, H. S., Ricketts, H. T., Singer, A. D., and McNeal, W. J.: Pellagra in Illinois. Condensed report of the Illinois Pellagra Commission, Arch. Int. Med., 1912, x, 123–168; 219–249.

37. Spies, T. D., and Sasaki, Y.: Unpublished observations. Quoted by: Spies, T. D., Bean, W. B., and Ashe, W. F.: Recent advances in the treatment of pellagra and associated deficiencies, Ann. Int. Med., 1939, xii, 1830–1844.

38. Sullivan, M. S.: Indican on the saliva of a case of pellagra complicated with tuberculosis, Jr. Biol. Chem., 1920, xli, p. lxx (Proc. Soc.).

39. Goldberger, J., and Wheeler, G. A.: The experimental production of pellagra in human subjects by means of diet, Hygienic Laboratory Bulletin, 1920, cxx, 7–116.

40. Myers, V. C., and Fine, M. S.: Metabolism in pellagra, Am. Jr. Med. Sci., 1913, cxlv, 705–720.

41. Hijmans van den Bergh, A. A., and Grotepass, W.: Porphyrinämie ohne Porphyrinuria, Klin. Wchnschr., 1933, xii, 586.

42. Najjar, V. A., and Holt, L. E., Jr.: The excretion of specific fluorescent substances in the urine in pellagra, Science, 1941, xciii, 20.

43. Najjar, V. A., and Wood, R. W.: Presence of a hitherto unrecognized nicotinic acid derivative in human urine, Proc. Soc. Exper. Biol. and Med., 1940, xliv, 386.

44. Kark, R., and Meiklejohn, A. P.: Pellagra and porphyrinuria, Am. Jr. Med. Sci., 1941, cci, 380.

STUDIES OF URINARY PIGMENTS IN PELLAGRA AND OTHER PATHOLOGICAL STATES. II. THE EXCRETION OF PORPHYRIN AND THE URO-ROSEIN REACTION IN DOGS WITH EXPERIMENTAL BLACKTONGUE [*]

By John A. Layne, M.D., and Cecil James Watson, M.D., F.A.C.P.,
Minneapolis, Minnesota

In the preceding paper [1] and in previous communications [2,3] it has been shown that the Beckh-Ellinger-Spies (B.E.S.) test [4] is due to urorosein and that positive reactions are correlated in all instances with positive Nencki-Sieber (N.S.) tests for urorosein. Distinct increases of coproporphyrin were noted in alcoholic,[2] but not in endemic pellagra.[1,3] Even in the former, · the amounts of porphyrin were insufficient to be productive of color in the B.E.S. test. In order to study the effect of nicotinic acid in the absence of complicating factors such as alcoholism or other coexisting disease, the following studies were carried out in dogs with blacktongue.

METHOD

Blacktongue was produced in female mongrel dogs, using the Goldberger diet No. 123.[5] The dogs were kept in metabolism cages to facilitate the collection of urine, but were allowed outside for exercise once daily. Precautions were taken in the care and cleaning of the cages to guard against contamination of the urine by feces insofar as this was possible. The urines were collected in 24 hour periods for the porphyrin determinations; petroleum ether was added to the collection bottles at the start of each period, as a preservative. When determinations for the other urinary pigments were carried out, toluene was used as the preservative, and the urines were usually examined within a few hours of passage in order to prevent changes due to bacterial growth.

The animals were observed for control periods of 16 to 20 days before the start of the blacktongue-producing diet. They were then maintained on this diet until they had developed a marked stomatitis, and had refused food for several days. Every animal exhibited evidence of blacktongue for at least one week before treatment was instituted. In all but one of the dogs, therapy consisted of the intramuscular administration of from 250 to 600 milligrams of nicotinic acid † and the replacement of the Goldberger diet by

the standard laboratory diet. In the remaining animal, the blacktongue-producing diet was continued, but a temporary regression of the oral lesions of the disease was produced by feeding three-fourths of a pound of fresh beefsteak after a severe attack of blacktongue had been produced. With the exception of one dog which died on the fifth day following treatment, the animals were observed for periods of not less than two weeks after treatment.

Coproporphyrin was determined by the modification of the Fikentscher method as described in paper I.[1] The Beckh-Ellinger-Spies test and the Nencki-Sieber test were performed in the same manner as described previously.[1] Toluene was added to 45 specimens of urine from three dogs with experimental blacktongue. The samples were collected at various stages of the disease and were allowed to stand in the light for periods of not less than three weeks. Twenty specimens of urine from three normal dogs were treated in a similar manner.

RESULTS

Porphyrin Determinations. Three dogs were used in this experiment. The daily excretion of porphyrin in the urine of these animals while on the standard laboratory diet during the control period varied from 27.6 to 81.3 micrograms of coproporphyrin for a 48 hour period of collection. With exception of dog number 1, in which there was a questionable rise, no significant change occurred in the daily excretion during the period of induction, the acute phase of the disease, or during the period of regression of the disease (table 1).

B.E.S. and N.S. Tests. In the normal dog, these tests were always negative if the urine was examined within a few hours of passage. If a few drops of 2 per cent solution of potassium nitrite were added to 10 or 20 c.c. of urine and the tests repeated, a reddish-purple color developed in the 25 per cent HCl in the B.E.S. test, or in the amyl alcohol in the N.S. test. If the urine was allowed to stand uncovered in the laboratory without a preservative for 24 hours or longer, frequently the B.E.S. and N.S. tests were positive without the addition of nitrite.

The pigment responsible for this color reaction in the urine of the dog has not been identified. A similar color reaction occurred in the urines from five of six normal dogs. This pigment differs from urorosein in that it has a more purplish color in 25 per cent HCl and in amyl alcohol, and that the spectroscopic absorption is much fainter in proportion to the color intensity of the solution. When a few drops of 2 per cent solution of potassium nitrite are added to dog urine and the B.E.S. test performed, extraction of the ether with a few cubic centimeters of 25 per cent HCl is followed by the production of a red-purple color. When examined spectroscopically, this acid solution exhibits a broad diffuse absorption band with maximum intensity at about 539–540 mμ. The edges of this band are poorly defined,

TABLE I

Urinary Excretion of Coproporphyrin, Expressed as Micrograms per Two Day Period of Collection, in Dogs Receiving a Blacktongue-Producing Diet

Number of days observed	Dog no. 1			Dog no. 2			Dog no. 3		
	Micrograms of copro-porphyrin	Weight in kilos	Remarks	Micrograms of copro-porphyrin	Weight in kilos	Remarks	Micrograms of copro-porphyrin	Weight in kilos	Remarks
			Control period			*Control period*			*Control period*
1– 2	50.3	18.4	Normal dog	27.6	14.1	Normal dog	70.4	11.8	Normal dog
3– 4	63.2								
5– 6	49.2			32.6			53.3		
7– 8	81.3								
9–10	61.2			52.1			48.9		
11–12	70.0								
13–14	42.1			38.9			57.6		
15–16	53.2								
17–18	61.7						68.3		
19–20	57.8	18.4			13.9			12.1	
			Blacktongue-producing diet started			*Blacktongue-producing diet started*			*Blacktongue-producing diet started*
1– 2	52.2			48.7			59.9		
3– 4	49.1								
5– 6	31.4			63.8			43.8		
7– 8	29.4								
9–10	69.2			28.6			56.9		
11–12	56.3								
13–14	39.6	19.1		29.4			93.8		
15–16	41.0								
17–18	50.6			47.6			46.8		
19–20	67.2								
21–22	73.0			38.3			57.1		
23–24	43.1							10.9	
25–26	60.3			50.4			50.4		
27–28	69.2								
29–30	88.6			22.3			63.6		
31–32	80.0								
33–34	73.3			43.3			74.6		
35–36	88.1	19.8	Mouth normal		14.1	Mouth normal		10.2	Mouth normal
37–38	60.3			18.8			64.7		
39–40	71.4								
41–42	89.3			38.7			53.7		
43–44	100.2							10.2	
45–46	73.8			43.8			70.4		
47–48	88.8								
49–50	54.1			39.3			63.6		
51–52	89.3	19.5	Mild inflammation of the buccal mucosa						Mild inflammation of the buccal mucosa

TABLE I (*Continued*)

Number of days observed	Dog no. 1			Dog no. 2			Dog no. 3		
	Micrograms of copro-porphyrin	Weight in kilos	Remarks	Micrograms of copro-porphyrin	Weight in kilos	Remarks	Micrograms of copro-porphyrin	Weight in kilos	Remarks
53–54	96.2						74.8	10.2	Severe blacktongue was present. Animal was very ill. Three-fourths of a pound of fresh beef steak was given to the dog; the Goldberger diet was continued
55–56	63.8			48.8	13.6	Mild inflammation of the buccal mucosa			
57–58	60.2	18.4	Stomatitis has become quite severe	58.3					
59–60	88.7								
61–62	66.3			47.9					
63–64	93.1			38.3					
65–66	79.9			48.3					
67–68	63.8								
69–70	77.1	17.3	Severe blacktongue was present. Goldberger diet was discontinued and normal diet resumed						
71–72				51.2		Severe blacktongue was present. Goldberger diet was discontinued and normal diet resumed			
73–74				46.3	13.0				
Period of regression of the blacktongue lesions									
1– 2	39.7			50.6		250 mg. of nicotinic acid were given during the first four days of treatment	59.2		Improvement of the stomatitis
3– 4	*			33.8					
5– 6				46.9					
7– 8				60.3			83.7	9.8	
9–10				38.8	13.9	All lesions of blacktongue had disappeared	76.3		
11–12				30.3					
13–14				50.8			68.4		
15–16				38.8					
17–18				46.3	13.9	Dog normal. No evidence of blacktongue	57.5	9.5	Inflammation of the mouth has subsided; the meat produced only a temporary remission of the disease, however

* This animal received 600 milligrams of nicotinic acid intramuscularly during the first four days of treatment, and the inflammation of the mouth had begun to subside. The dog died suddenly, however, about 100 hours after the start of therapy; the cause of death was undetermined. Urine collection during the last two day period was incomplete.

but have been measured at 532 to 556 mμ. The pigment is not extracted from ether with 5 per cent HCl, and only to a slight extent with 10 per cent HCl.

This red pigment can be extracted readily with amyl alcohol from the dog's urine following treatment with nitrite and 25 per cent HCl. In amyl alcohol a faint, diffuse absorption band is noted with maximum intensity at 539 mμ. The presence of other pigments, however, such as indican and urobilin, frequently masks the red color in the amyl alcohol.

The metabolism of tryptophane is different in the dog from in man in that kynurenic acid is a normal constituent of the urine of the former, whereas it is doubtful if this substance is formed in man. It occurred to us, therefore, to determine whether kynurenic acid might be responsible for the above-mentioned color reaction in the dog's urine. However, aqueous solutions of kynurenic acid * to which KNO_2 had been added failed to exhibit any color in either the B.E.S. or N.S. tests.

The B.E.S. and N.S. tests were carried out on the urines of three dogs during the stage of induction of blacktongue, in the acute phase as well as during a control period before and after the period of feeding the Goldberger diet. Both tests were negative throughout. Spies and his associates[6,7] have likewise noted that the urine from dogs with spontaneous blacktongue does not give a positive B.E.S. test.

The toluene preservative remained clear in 39 of the urines from the three dogs with blacktongue. In the remaining six, a red color developed in the preservative. No correlation could be established between the severity of the disease at the time the urine was collected and the appearance of the red pigment in the toluene. The feeding of three-fourths of a pound of fresh beefsteak to one dog was not associated with the development of a red color in the toluene. In 12 of the urines from the normal dogs, the toluene remained clear, whereas a red color developed in the remaining eight. It appears from these observations, therefore, that the development of a red color in the toluene preservatives of dog urines is not correlated with nicotinic acid deficiency. The characteristics of two red pigments which were present in the toluene will be described in a separate communication.

CONCLUSIONS

1. The spontaneous urorosein reaction was consistently negative in urine samples from dogs having experimental blacktongue.

2. The appearance of red color in the toluene preservatives of dog urines was not correlated in any way with nicotinic acid deficiency.

3. There was no significant increase in coproporphyrin excretion in dogs with blacktongue over that observed during the control periods.

* Samples of kynurenic acid were obtained through the courtesy of Hoffmann-La Roche, Nutley, New Jersey, and Dr. Clarence P. Berg, State University of Iowa, Iowa City, Iowa.

BIBLIOGRAPHY

1. WATSON, C. J., and LAYNE, J. A.: Studies of urinary pigments in pellagra and other pathological states. I. Clinical observations, ANN. INT. MED., 1943, xviii, 183–199.
2. WATSON, C. J.: The urinary pigments in four cases of alcoholic pellagra, Proc. Soc. Exper. Biol. and Med., 1938, xxxix, 514–518.
3. WATSON, C. J.: Further observations on the red pigments of pellagra urines, Proc. Soc. Exper. Biol. and Med., 1939, xli, 591–595.
4. BECKH, W., ELLINGER, P., and SPIES, T. D.: Porphyrinuria in pellagra, Quart. Jr. Med., 1937, vi, 305–319.
5. GOLDBERGER, J., WHEELER, G. A., LILLIE, R. D., and ROGERS, L. M.: A further study of experimental blacktongue with special reference to the blacktongue preventive in yeast, Pub. Health Rep., 1928, xliii, 657–694.
6. SPIES, T. D., ARING, C. D., GELPERIN, J., and BEAN, W. B.: The mental symptoms of pellagra. Their relief with nicotinic acid, Am. Jr. Med. Sci., 1938, cxcvi, 461–475.
7. SPIES, T. D., VILTER, R. W., and ASHE, W. F.: Pellagra, beriberi and riboflavin deficiency in human subjects, Jr. Am. Med. Assoc., 1938, cxiii, 483–486.

STUDIES OF URINARY PIGMENTS IN PELLAGRA AND OTHER PATHOLOGICAL STATES. III. CERTAIN TOLUENE SOLUBLE PIG- MENTS OF HUMAN AND CA- NINE URINE [*]

By Samuel Schwartz, M.D., James F. Marvin, M.S., John A. Layne, M.D. and Cecil James Watson, M.D., F.A.C.P., *Minneapolis, Minnesota*

Toluene preservatives of urine from pellagrins and from certain other patients suffering from malnutrition of one cause or another have been observed in many instances to develop a pink or deep red color upon standing.[1, 2, 3] The development of this red pigment appears not to depend upon the presence of nicotinic acid deficiency, since it was observed in the preservatives of urines from patients who did not have any evidence of this deficiency.[3] No change was seen in the toluene preservatives of 72 urines from 54 individuals who were normal, or who had arthritis, but no evidence of other disease. In an earlier investigation, Watson[2] had noted that the characteristics of the red pigment extracted by the toluene corresponded closely with those of indirubin or indigo red. Since further study showed that often more than one red pigment was extracted by the toluene, it seemed advisable to investigate these substances in more detail.

METHOD AND MATERIALS

Human Urine. Ten cubic centimeters of toluene were added to about 150 c.c. of urine, which was allowed to stand in the light for a period of at least three weeks and observed for the development of a red color in the toluene layer. The urines were obtained from a number of patients who had clinical evidence of nicotinic acid deficiency, from seven patients who had squamous cell carcinoma of the cervix uteri, and who were receiving deep roentgen therapy, as well as from a number of patients who were in the hospital because of one condition or another (see paper I). All of the toluene preservatives which became pink or red were pooled and were concentrated in vacuo to a small volume. The pigments were taken up in a small amount of ethyl acetate, to which was added 20 parts of petroleum ether. This solution was passed through a column of Brockmann's Al_2O_3 [†] according to the usual method of preparing a flowing chromatogram. A number of different pigments were separated in this manner (figure 1). By means of elution with increasing concentrations of ethyl acetate in petroleum

ether, the two red pigments (6 and 7 in figure 1) were isolated. They were purified further by passage through a new column of Al_2O_3, and were recrystallized out of hot ethyl acetate.

Canine Urine. Toluene was added to 45 specimens of urine from three dogs in which experimental blacktongue had been produced by the feeding of Goldberger diet No. 123 (as described in paper II). The samples of urine were collected at various stages of the disease and were allowed to stand in the light for periods of not less than three weeks. In 39 specimens

COLOR OF ZONE		PIGMENT REMOVED BY ELUTION WITH
	Brown	
Pigment 6	Red-orange	Ethyl acetate
Pigment 7	Red-violet	{ Petroleum ether / Ethyl acetate } equal parts
	Brown	{ Petroleum ether 10 parts / Ethyl acetate 1 part
	Blue-green	{ Petroleum ether 19 parts / Ethyl acetate 1 part
	Orange	Petroleum ether
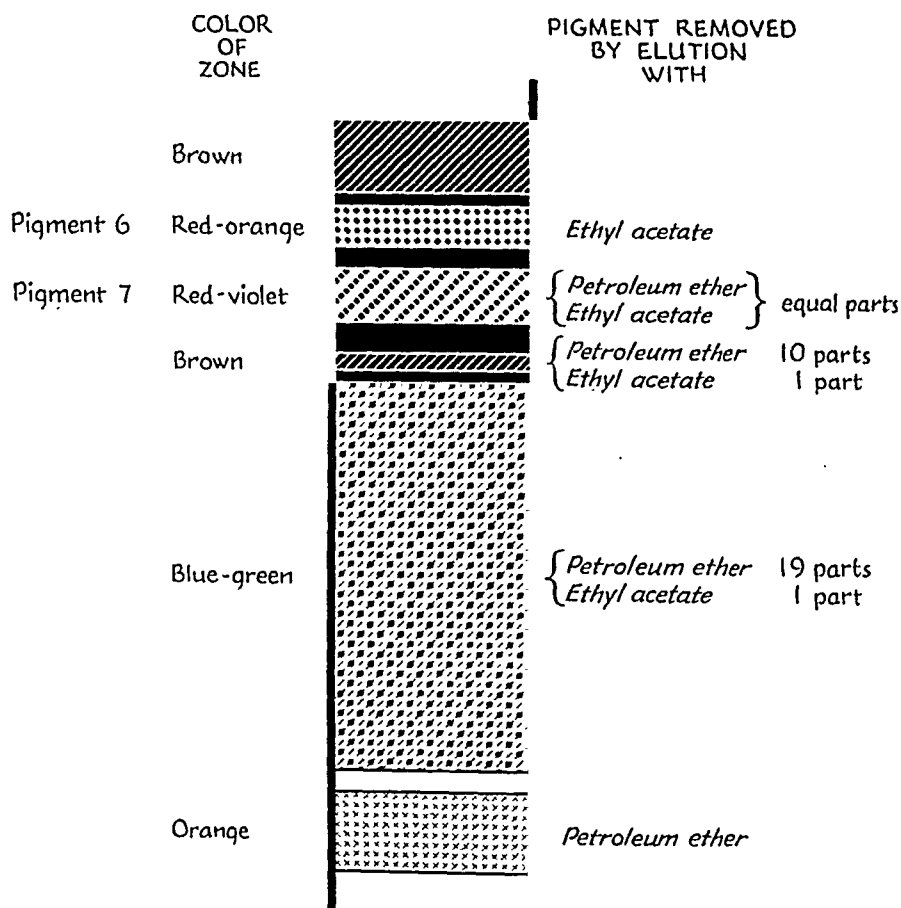
FIG. 1. Chromatographic separation of toluene soluble pigments from human urine.

the toluene remained clear; in the remaining six a red color developed in the preservative. As stated in paper II, no correlation was apparent between the severity of the disease at the time the urine was collected and the development of the red pigment. The toluene preservatives of eight from a group of 20 specimens of urine from three normal dogs developed a similar red color.

The red toluene preservatives from the 14 specimens of urine were combined and were concentrated in vacuo to less than five cubic centimeters. The residue was dissolved in 15 c.c. of ethyl acetate and was made up to 400

c.c. with petroleum ether.   This solution was passed through a column of Al$_2$O$_3$ in the usual manner.   The red and violet pigments (4 and 5 in figure 2) were purified by passage through a new column of Al$_2$O$_3$ and by repeated crystallization.

Synthetic Indirubin.   A small quantity of indirubin* which had been synthesized from isatin and indoxyl, was dissolved in ethyl acetate, to which was added nine parts of petroleum ether, and this solution was passed through
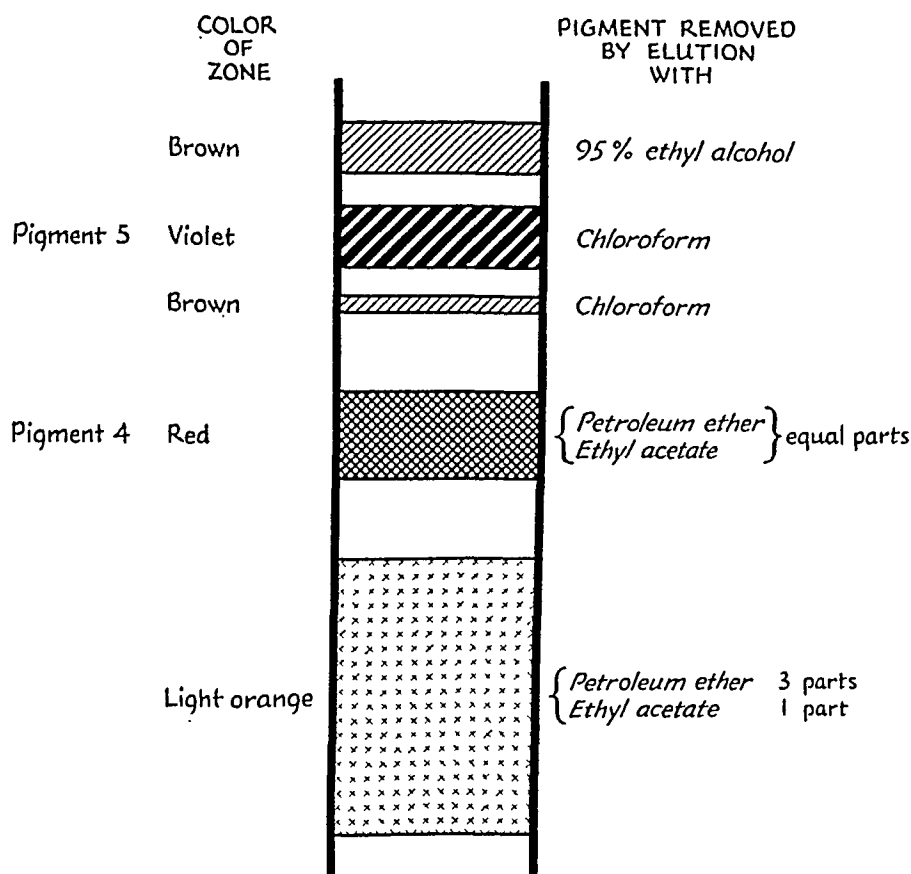
FIG. 2. Chromatographic separation of toluene soluble pigments from canine urine.

a column of Al$_2$O$_3$.   All of the pigment was adsorbed on the top of the column, however, and elution with increasing concentrations of ethyl acetate in petroleum ether, up to equal parts of the two solvents, resulted in little change in their position.   Elution with chloroform resulted in the chromatogram represented in diagrammatic form in figure 3.

Studies of the absorption of the pigments in the ultraviolet region of the spectrum were carried out by the photographic method with a Hilger quartz prism spectrograph and a Judd-Lewis spectrophotometer.   The synthetic

* The indirubin used in this study was obtained through the courtesy of Dr. E. K. Bolton, Chemical Director, E. I. du Pont de Nemours and Company, Wilmington, Delaware.

indirubin was dissolved in absolute ethyl alcohol in a concentration of 1.175 milligrams per 100 c.c. (4.5×10^{-5} moles per liter).

The concentration of the natural red or violet pigments, as isolated from urine, was adjusted to approximately the same absorption at the maximum near 290 mμ. Cells of 1.0 and 0.2 centimeter length were used with each solution. The scale is the logarithm of the molecular extinction coefficient for synthetic indirubin (prior to chromatographic analysis) (pigment 1, figure 4). The curves for the other solutions were shifted so that the values at the maximum near 290 mμ exactly matched that for indirubin. All
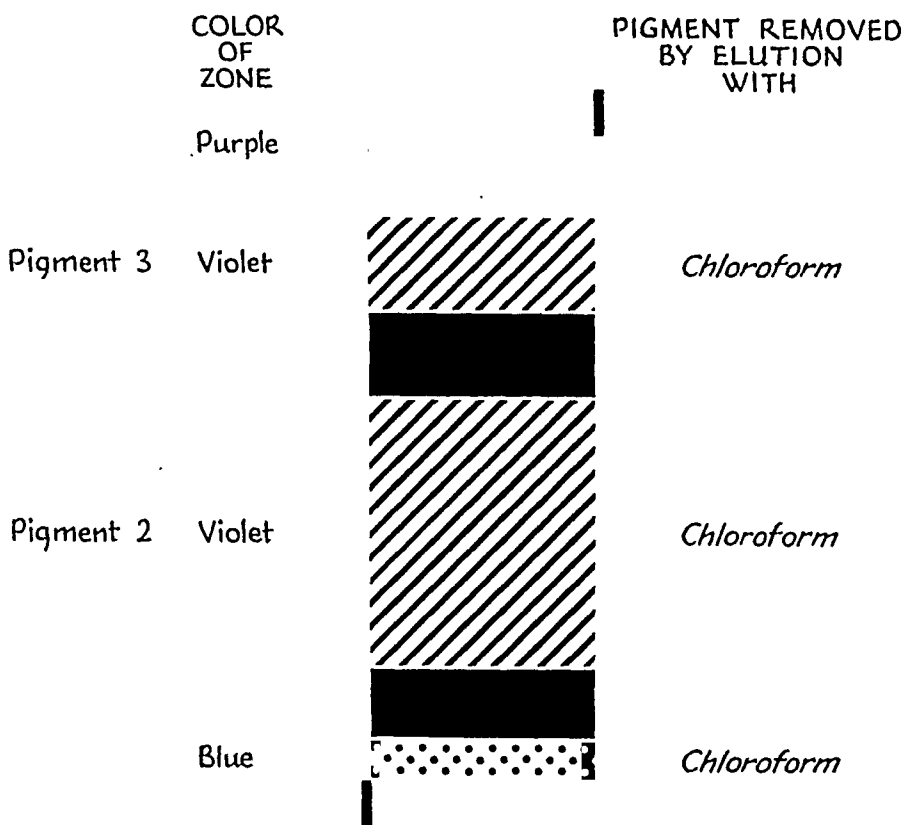
FIG. 3. Chromatographic separation of components of crude synthetic indirubin.

measurements were made with freshly prepared solutions, since solutions of pigments VI and VII were observed to be unstable. The spectrum of pigment VII (taken after several weeks) showed a broad absorption band between 410 mμ and 450 mμ which was not present in the spectrum of the freshly-prepared solution.

Sublimation temperatures were observed in the following manner: crystals of the sample being studied were placed on a round cover slip as usually employed for micro-melting point determinations with the Fisher-Johns apparatus.* After placing the cover slip in the well of the apparatus, it is

* Fisher Scientific Company, Pittsburgh, Pa.

covered with a glass slide which bridges the well, leaving an air space of about 2 mm. between cover slip and slide. As the temperature rises, it is now possible to note the beginning of sublimation by means of focusing on the under surface of the glass slide and observing the first appearance of crystals there. It is believed that this affords a much sharper method of comparing sublimation temperatures than hitherto available.
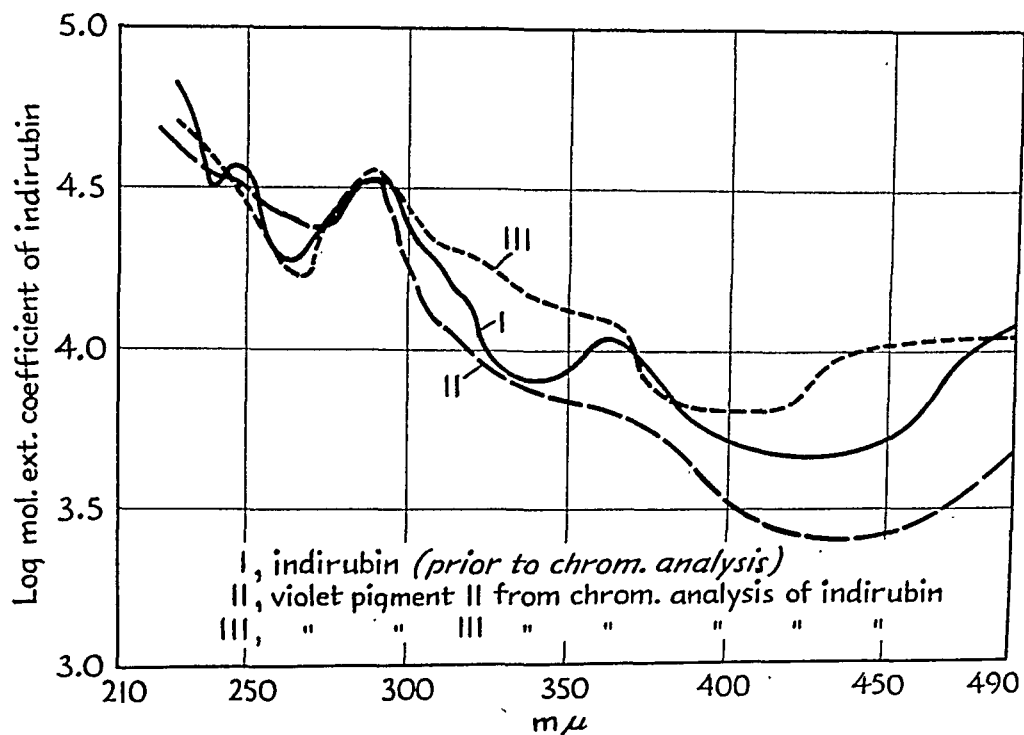
Fig. 4. Ultraviolet spectral distribution curves of crude synthetic indirubin and component substances as separated by chromatographic analysis.

OBSERVATIONS

Six pigments were present in the toluene extract of the human urines, as demonstrated by their behavior on the column of Al_2O_3 (figure 1), and five pigments were separated from the toluene extracts of canine urine (figure 2). The absorption in the ultraviolet region of the four red or violet pigments is shown in figure 5. Pigment 4 (dog urine) and pigment 7 (human urine) had a similar, although not identical absorption in the ultraviolet region and behaved in a similar manner on the Al_2O_3 column. The absorption of the other colored pigments was not studied.

Two distinct violet pigments were separated by the passage of the synthetically prepared indirubin through the Al_2O_3 column. The absorption of these two pigments in the ultraviolet region differed from one another and from the absorption of the "whole" indirubin (figure 4). The absorption of the latter agrees closely with that reported previously by Cholewinski and Marchlewski.[4]

The following sublimation temperatures were observed:

Crystals	Temperature at which sublimation was first noted (first crystals appeared on slide)	Comment
1. Crude indirubin (before chromatographic analysis)	188° C.	Large, curving and branching needles at first. Rosettes of straight needles at 250° C.
2. Pigment 3 (from synthetic indirubin), figure 3	172° C.	Crystals had disappeared from cover slip above 235° C.
3. Pigment 7 (from human urine), figure 1	153° C.	Crystals had disappeared from cover slip above 225° C.

When dissolved in absolute alcohol all of the seven red or violet pigments exhibited a light blue fluorescence in ultraviolet light.   Solutions of pigments
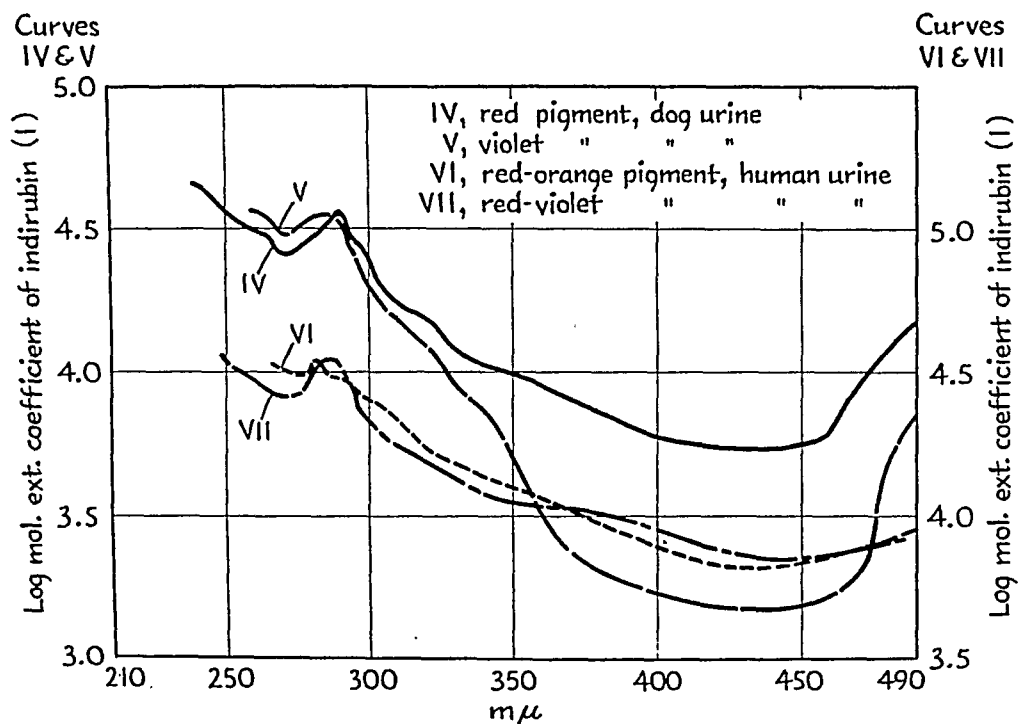
FIG. 5.   Ultraviolet spectral distribution curves of the red and violet toluene soluble pigments from human and canine urines.

VI and VII which had stood in the light for over a month gave a green or bluish green fluorescence when reëxamined.   The fluorescence of the other pigments did not change on standing.

DISCUSSION

It is evident from the results just given that none of the red or violet pigments isolated from the toluene extracts of either human or canine urines was identical with synthetic indirubin.   Chromatographic analysis, ultraviolet spectral distribution curves, and sublimation temperatures of the latter substance revealed clearly that neither the crude indirubin nor its component

pigments were identical with the human or canine pigments. At the same time, it appears that they are all closely related substances. For the time being it can only be stated that the natural pigments are indirubin-like in character.

SUMMARY AND CONCLUSIONS

1. The red pigment extracted by toluene from certain human and canine urines (papers II and III) has been shown by means of chromatographic analysis to be composed of several similar pigments.

2. Two pigments each from human and canine urines were found very similar to, but not identical with, synthetic indirubin. On the basis of chromatographic analysis and spectral distribution curves, the latter was likewise shown to be a mixture of related pigments, none of which was entirely identical with any of those from the urine.

BIBLIOGRAPHY

1. WATSON, C. J.: The urinary pigments in four cases of alcoholic pellagra, Proc. Soc. Exper. Biol. and Med., 1938, xxxix, 514–518.
2. WATSON, C. J.: Further observations on the red pigments of pellagra urines, Proc. Soc. Exper. Biol. and Med., 1939, xli, 591–595.
3. WATSON, C. J., and LAYNE, J. A.: Studies of urinary pigments in pellagra and other pathological states. I. Clinical observations, ANN. INT. MED., 1943, xviii, 183–199. II. The excretion of porphyrin and the urorosein reaction in dogs with experimental blacktongue, ANN. INT. MED., 1943, xviii, 200–205.
4. CHOLEWINSKI, J., and MARCHLEWSKI, L.: Absorption kurzwelligen Lichtes durch Indirubin und Indigotin, Biochem. Ztschr., 1938, ccc, 56.

DUPUYTREN'S CONTRACTURE AS A SEQUEL TO CORONARY ARTERY DISEASE AND MYOCARDIAL INFARCTION *

By KENNETH C. KEHL, M.D., F.A.C.P., *Racine, Wisconsin*

REPORTS of Dupuytren's contracture in association with disease of the coronary arteries have been infrequent. Askey,[1] in reviewing the syndrome of painful disability of the shoulder and hand following coronary occlusion, suggested the possible relationship of changes in the palmar aponeurosis and myocardial infarction. To the seven cases described by him are added the six cases here presented, and points of difference and similarity are noted.

CASE REPORTS

Case 1. P. H., a 48 year old white male, a laborer, in April 1936, complained that since 1931 he had noted abdominal distention, belching, flatulence, and cramping lower abdominal pain which had recurred at irregular intervals. These symptoms were aggravated by taking high roughage foods, especially during periods of mental or emotional stress. At this time there were no symptoms considered to be referable to the heart.

The family history was irrelevant. At the age of 18 years he had had migratory joint pains involving both the upper and lower extremities, associated with fever and requiring bed rest. He had had pneumonia in infancy and again at the age of 16 years.

Examination when he was first seen revealed slight tenderness over the cecum and sigmoid and moderate gaseous distention. A soft, systolic apical murmur was present without demonstrable cardiac enlargement. There was no evidence of cardiac decompensation. In view of the rheumatic history the cardiac findings were thought possibly to indicate a rheumatic mitral lesion.

He was not seen again until May 12, 1939, when he was admitted to the hospital in acute left ventricular failure. For about one year prior to that time he had noted dyspnea of mild degree on exertion, cough, excessive fatigue, nocturia and nervousness, but he had been able to continue at his rather heavy work.

On examination the heart was definitely enlarged to the left with a regular rhythm and a rate of 80 per minute. A loud, rough, systolic aortic murmur was heard followed by a faint aortic second sound. There was also a rough murmur at the apex obscuring the first sound. The blood pressure was 132 mm. Hg systolic and 80 mm. diastolic. Occasional moist râles were found in both bases. No enlargement of the liver was noted and there was no peripheral edema.

During the week following his admission to the hospital there was at no time any elevation of temperature or leukocytosis.

An electrocardiogram taken on May 23, 1939, showed slight slurring of the QRS complexes in all the standard leads. ST_1 was isoelectric and T_1 of very low voltage. ST_2 and ST_3 were coved and depressed. T_2 and T_3 were inverted. Left axis deviation was present. Lead IV showed no significant deviation from normal. The impression was myocardial infarction, posterior type.

He improved on bed rest, sedation, and aminophyllin and his convalescence was uneventful until July 10, 1939, when he again experienced nocturnal paroxysmal

dyspnea. At this time he noted the onset of the aching pain in the left clavicle and left shoulder. Shortly following his discharge from the hospital on August 12, 1939, a thickened area in the palmar fascia of the right hand at the base of the little and ring fingers, resembling an early Dupuytren's contracture, was discovered. The thickening in the palmar fascia of the right subsequently progressed to a typical Dupuytren's contracture of marked degree. About four months later changes were noted in the left palm and since then they progressed until the contracture was about equal bilaterally. During the period over which the contractures were developing he suffered from a more or less constant aching pain in both shoulders. Motion at the shoulder, especially abduction and external rotation, was limited and painful in both arms and there was tenderness to pressure over the shoulder joints and lateral aspects of the arms. At the time of the development of the Dupuytren's contracture there was aching in the hands but no redness or swelling was noted. Numbness, tingling and coldness of the hands also were complained of at that time.

Following his discharge from the hospital he had frequent episodes of acute left ventricular failure and he had been a cardiac invalid since May 1939. The shoulder disability remained such that he required assistance in dressing and undressing.

He was reëxamined in June 1941, slightly more than two years after coronary occlusion, with the following findings: The fingers of both hands were livid and cold to the touch. A marked arcus senilis was present and the ocular fundi showed thickened and tortuous arteries. Temporal arteries were prominent, tortuous and definitely thickened. A nodular enlargement of the thyroid was palpable. Moist râles were heard in the right lung base posteriorly and laterally. The heart was enlarged to the left and downward. The apex impulse was barely perceptible but well localized. The cardiac rhythm was regular except for very rare premature contractions. The rate was 72 per minute. The first sound at the apex was replaced by a blowing murmur. Along the left of the sternum a rough systolic murmur was heard which was of maximum intensity at the aortic area. This murmur was transmitted into the neck. The second aortic sound could not be heard. The blood pressure was 144 mm. Hg systolic and 86 mm. diastolic. There was no enlargement of the liver or evidence of peripheral edema. Kahn test was negative. Blood and urinary findings were not exceptional. The basal metabolic rate was within normal limits.

Both hands showed the classical picture of Dupuytren's contracture of an advanced degree (figure 1). The skin of the palms was thrown into deep folds and ridges, thickened and firmly adherent to the underlying aponeuroses. Although flexion was only slightly impaired, it was impossible to extend completely the ring or little fingers of either hand. The shoulders remained painful and tender, and motion continued to be limited.

An electrocardiogram taken on June 9, 1941, showed the following: Slurring of the QRS complexes persisted in the standard leads. T_1 remained upright with the voltage slightly increased. T_2 had become diphasic. ST_3 remained slightly coved and T_3 was inverted to a lesser degree. Left axis deviation was more marked with decreased R_3 and increased S_3 voltage. Lead IV remained practically unchanged.

In January 1942 the contractures in the palms had progressed until all fingers of both hands were involved.

Case 2. T. B., a 40 year old white male, an advertising executive, was seen for the first time on May 10, 1939. On the previous evening, following a heavy meal, he had experienced a severe precordial pain, crushing in character, that radiated down both arms into the fingers and also up into the neck. The pain was attended by dyspnea, cyanosis, cough, and a moderate degree of shock. Large doses of opiates given over a period of 14 hours were necessary to control the pain. He had considered himself in good health prior to the onset and had had no pain or other symptoms referable to the heart. There was no rheumatic history.

When examined there was obvious dyspnea and orthopnea with a moderate degree of cyanosis. The skin, which showed a gray pallor, was moist and cold. The lungs were filled with wet râles. The heart was normal in size. The rhythm was regular and the rate 102 per minute. The heart sounds were distant and of poor quality. A soft, systolic murmur was audible at the apex. The blood pressure was 90 mm. Hg systolic and 62 mm. diastolic. The liver was at the costal margin and there was no evidence of peripheral edema.

He was placed in an oxygen tent and was treated with opiates, aminophyllin, hypertonic glucose and mercurial diuretics. He responded well and was soon quite comfortable and relieved of the dyspnea and cyanosis. A slight elevation in temperature persisted during the first week and the sedimentation rate was increased.

An electrocardiogram taken on May 10, 1939, revealed the following: There was regular sinus rhythm. The rate was 102 per minute. Intervals were normal. P_1 was notched and P_2 was broadened. QRS was of low voltage in the standard leads. There was left axis deviation. ST_1 was isoelectric. T_1 was small and inverted. ST_2 was slightly elevated. T_2 was small but erect. ST_3 was isoelectric. T_3 was very small and erect. ST_4 was displaced upward 0.6 cm. T_4 was sharply inverted. QRS_4 was monophasic and directed downward. Impression was myocardial infarction, anterior type.

Following the coronary occlusion his recovery was uneventful until August 1939, when he first noted pain of the persistent aching type in the left shoulder and arm. Abduction and external rotation were limited and painful, and there was tenderness in the shoulder joint and in the region of the deltoid insertion. At the time of the shoulder disability he also noted numbness and tingling in the fingers of both hands, associated with stiffness in the phalangeal joints. There was also lividity of the palms of both hands, especially of the palmar surfaces of the fingers. The pain was relatively intractable and persisted in the left shoulder for more than 20 months, disappearing very slowly. Pain appeared in the right shoulder eight months after the onset of the disability in the left shoulder and persisted in that region to a slight degree. The numbness, tingling and stiffness of the hands were of short duration and at no time was redness or swelling noted. However, the discoloration of the palmar surfaces persisted.

In April 1941, palmar changes of the Dupuytren's type were noted for the first time. A small, firm nodule about 1 cm. in diameter had appeared at the base of the ring finger of the right hand. By October 1941 this nodule had increased in size and there was puckering of the overlying skin although no contracture was present. The left palm showed no evidence of changes.

Late in November 1941, for the first time he began to have cramping pains in the calves of both legs. The pains were brought on by walking and were quickly relieved by rest. No changes in the pulsation of the arteries of either leg could be found. The leg pains subsided somewhat but excessive exercise still caused some discomfort.

Case 3. T. C., a 46 year old white male, real estate salesman, was seen first on November 27, 1937, when he complained of precordial pain. The pain, which was moderately severe and constricting in character, radiated from the precordium into the right arm and, when especially severe, into both arms. Slight exertion precipitated the pain which had occurred almost daily for the two weeks prior to his first visit. Slight dyspnea on exertion, palpitation, tachycardia and occasional irregularities of cardiac rhythm had been noted. The family history was irrelevant and there was no history of rheumatic fever.

Physical examination at the time of the first visit revealed a blood pressure of 192 mm. Hg systolic and 140 mm. diastolic. There was no evidence of cardiac enlargement. The second aortic sound was accentuated. No murmurs were heard. The cardiac rhythm was interrupted by occasional premature contractions. No evidence of decompensation was found.

An electrocardiogram taken November 27, 1937, revealed the following: There was a normal sinus rhythm. The rate was 92 per minute. Intervals were normal. There was marked left axis deviation. ST_1 and ST_2 were slightly depressed. QRS_2 and QRS_3 were slurred. T_3 was diphasic. No chest lead was recorded.

While under treatment he remained relatively free from pain until shortly after the death of his wife in November 1938. The pain then recurred with increased frequency and severity and now for the first time awakened him from sleep. Following an especially severe attack of pain of two hours' duration on November 15, 1938, the blood pressure fell from 180 mm. Hg systolic and 115 mm. diastolic to 150 mm. systolic and 100 mm. diastolic, and he was hospitalized. At this time he was very apprehensive, slightly dyspneic, pale and exhausted. Occasional moist râles were heard at the lung bases. The heart was borderline in size. The rate was 93 per minute. The cardiac rhythm was interrupted by frequent premature contractions. The quality of the heart sounds had become poor, and a soft systolic murmur was present at the apex. There was no enlargement of the liver or peripheral edema.

An electrocardiogram taken on November 15, 1938, revealed the following changes: Frequent ventricular premature contractions were present. The T voltage in the standard leads was reduced. ST_1 and ST_2 were more definitely depressed. T_1 was diphasic. ST_3 was slightly elevated. T_3 was diphasic. ST_4 was slightly depressed. T_4 was inverted. A coronary occlusion with myocardial infarction was suspected.

During the week following there was a slight elevation in temperature and the sedimentation rate was increased. Opiates and intravenous papaverine controlled the severe pain. An electrocardiogram taken at an interval of one week, on November 22, 1938, showed some changes to have occurred during that time. ST_1 was slightly depressed and followed by an erect T_1 of very low voltage. ST_2 was slightly elevated and coved. T_2 was inverted and of low voltage. ST_3 was elevated to a more marked degree and was definitely coved, followed by a small inverted T_3. Lead IV showed no change.

After being without pain for one week, he was discharged to his bed at home on November 25, 1938. He continued quite comfortable and free from pain until the end of December when an attempt was made to get him out of bed by the usual easy stages. At that time the pain recurred with such frequency and severity that it necessitated his return to complete bed rest. Tissue extract was added to the aminophyllin, nitrites and sedatives he had been receiving but without striking response and he was again hospitalized. The findings in the heart remained as on the previous admission. The blood pressure, however, had fallen to 112 mm. Hg systolic and 80 mm. diastolic. There was no elevation of temperature, no leukocytosis, no increase in sedimentation rate at this time. Again an electrocardiogram revealed changes suggesting progressive involvement of the myocardium.

Changes in the palms of the hands were noted for the first time during this admission, although they must have been present for some time prior to this discovery. Attention was drawn to the hands because of pain, swelling and stiffness of the finger joints. In the left palm, at the base of the ring and little fingers, definite thickening and puckering of the skin was found but without evidence of contracture. On the right, again at the base of the ring and little fingers, thickening and puckering of the skin of more marked degree was noted and a beginning contracture was present. Motion of the fingers, although painful, was complete except for the ring and little fingers of the right hand which could not be extended completely. Some bluish mottling of the palms and palmar surfaces of the fingers was noted. At no time were the shoulders the site of the aching constant type of pain. However, during the attacks of precordial pain, the pain in the hands was usually aggravated. On several occasions the pain originated in the hands and radiated to the precordium.

In spite of all therapy the attacks of pain continued to occur from eight to 12 times daily and he finally sought relief elsewhere on March 8, 1939. He received some temporary relief there while being given "Cortiode" but on April 23, 1939, during a severe attack of pain, he died.

Pertinent necropsy findings were as follows: The heart weighed 430 grams. The coronary arteries were thickened with numerous calcified areas throughout, especially in the anterior descending branch of the left coronary artery. This vessel was completely occluded 2 cm. from its orifice by a fresh thrombus. The right coronary artery showed considerable thickening and calcification but was patent throughout. An old organized thrombus was found at the tip of the left ventricle and the cut surface showed much scarring in that area. The valves of the heart were not remarkable.

At practically every orifice of the smaller arteries coming off of the aorta, there was marked nodular thickening with considerable plaque formation and longitudinal streaking.

The microscopic examination showed marked arteriosclerotic changes in practically all tissues examined.

Case 4. N. J., a 60 year old, white male, a retired executive, had suffered from substernal pain for five months when seen for the first time on July 9, 1937. The pain, severe and constricting in character, radiated from the upper sternum into both arms. The episodes of pain, varying in duration from 15 minutes to one hour and occurring from one to three times daily, were precipitated by exertion. Especially severe attacks were accompanied by mild nausea and moderate dyspnea.

At the age of 46 years the patient was said to have had "inflammatory rheumatism" and had been told that the heart had become involved. He had retired at 50 years of age and had done no work since.

Examination at the time of the first visit revealed a moderately obese male, quite well preserved. There was no evidence of exceptional arteriosclerosis. The heart was enlarged to the left and downward. The rhythm was regular with a rate of 92 per minute. The heart sounds were distant and a soft systolic murmur was heard at the apex. The blood pressure was 190 mm. Hg systolic and 90 mm. diastolic. There were no signs of congestive failure.

An electrocardiogram taken July 10, 1937, showed regular sinus rhythm with a rate of 90. The PR interval was prolonged to 0.24 second. P_2 was notched. The QRS was slurred in the standard leads with marked splintering in Lead III. T_1 was inverted. There was no significant displacement of ST in any lead. T_2 and T_3 were erect. The fourth lead was not recorded. The electrocardiographic findings were considered to be due to coronary sclerosis and the resultant myocardial ischemia. There was little to substantiate a diagnosis of rheumatic heart disease.

Under treatment he remained fairly comfortable except for occasional attacks of pain until early in 1941. In July 1941, after not having been seen for some time, he complained of extreme dyspnea, repeated severe attacks of precordial pain, disagreeable palpitation, cough, orthopnea, swelling of the ankles and excessive fatigue, all of which had been present for several months. His condition had become so desperate that he hesitated to seek aid because of his fear of what the prognosis might be.

At this time physical examination revealed auricular fibrillation and advanced cardiac decompensation.

An electrocardiogram recorded August 1, 1941, revealed the following: Auricular fibrillation was present. QRS was slurred in all leads. QRS_3 and QRS_4 showed notching. ST_1 was slightly depressed. T_1 was inverted and of very low voltage. ST_2 was depressed. T_2 was inverted. ST_3 and T_3 were isoelectric. QRS_4 was monophasic with no Q or S element. ST_4 was elevated very slightly. T_4 was

erect but of low voltage. It was thought that myocardial infarction probably had occurred some time during the previous three months.

Although he was unaware that changes had taken place in his hands, small, firm nodules were present at the bases of both ring fingers. The nodules were about 0.8 cm. in diameter and were not adherent to the deeper structures. There was no contracture and he had not noted pain, swelling or circulatory changes in the hands. Careful questioning failed to disclose a history of shoulder pain other than that referred to the shoulder from the precordium during attacks of angina pectoris.

Subsequently during the course of digitalization he developed a hemiplegia, probably due to cerebral embolism, and died.

Case 5. F. J., a 59 year old, white male, a mechanic, was seen for the first time in June 1941, when he complained of precordial aching, dizziness and shortness of breath on exertion. During the previous winter he had noted dyspnea, substernal oppression and non-productive cough, brought on by exertion during cold weather. In May 1941, while at work, he suddenly became dyspneic and lost consciousness for an unknown period. In spite of the weakness and excessive fatigue that persisted after this experience he returned to his work. About four weeks later he experienced a similar episode on the way home from work, becoming dyspneic and cyanotic and losing consciousness for about 20 minutes. Oxygen was administered by a "rescue squad" and he was removed to his home. Dyspnea when at rest and some substernal aching persisted but he again returned to work until the severity of his symptoms made it impossible for him to continue. He was seen for the first time 10 days after the last episode.

Physical examination revealed a well developed and slightly obese white male who was dyspneic on slight exertion. The mucous membranes were slightly cyanotic. The neck veins were distended moderately. Moist râles were heard at both lung bases. The heart was enlarged to the left and downward. The rhythm was regular with a rate of 108 per minute. The heart sounds were of only fair quality with a rough, high-pitched systolic murmur at the aortic area, transmitted to the apex. The blood pressure was 146 mm. Hg systolic and 82 mm. diastolic. The liver edge was at the right costal margin and minimal pretibial edema was noted.

An electrocardiogram taken on June 20, 1941, revealed regular sinus rhythm and normal intervals. There was marked left axis deviation. The QRS was slurred slightly in all leads. ST_1 was depressed with an inverted and coved T_1. ST_2 was depressed with a diphasic T_2. ST_3 was elevated with an erect and coved T_3. ST_4 was depressed with a diphasic T_4. It was the impression that infarction of the myocardium had occurred recently.

The past medical history was irrelevant with the exception of painful swelling of the ankles at 28 years of age, which had necessitated two weeks of bed rest. The details of this illness were obscure.

Under treatment his condition improved and he remained quite comfortable until early in August when he noted pain and stiffness in the shoulders and pain over the lateral aspect of the upper arm. The shoulder disability was soon followed by stiffness, swelling and numbness in both hands. Redness and lividity were not noted. In October thickening of the skin of the palms was observed. The right palm was involved at the base of the index and of the little fingers where the depth of the normal palmar folds was increased and the skin had become puckered. The left palm showed similar changes at the base of the ring finger. The condition has been slowly progressive since that time.

Case 6. R. S., a 70 year old, white housewife, was seen for the first time on May 25, 1941, complaining of pain in the left upper abdomen, nausea, vomiting and prostration. The temperature was elevated to 100.6° F., and there was a leukocytosis. The cardiac findings were essentially negative. The heart was regular with a rate

of 70 per minute. The blood pressure was 100 mm. Hg systolic and 72 mm. diastolic.

On the following day the pulse rate had increased to 110 per minute, and there were occasional premature contractions. At this time a systolic murmur was heard over the apex and there was also a pericardial friction rub in this area.

An electrocardiogram taken on May 26, 1941, showed the following: Regular sinus rhythm was present with the rate of 100 per minute. QRS was slurred in the standard and chest leads. ST_1 was slightly elevated. T_1 was inverted and of low voltage. ST_2 was isoelectric. T_2 was erect. ST_3 was isoelectric. T_3 was erect. QRS_4 was monophasic and inverted. ST_4 was elevated with inverted T_4. The interpretation was myocardial infarction.

After two weeks of satisfactory progress the patient became desperately ill. There were now frequent episodes of auricular fibrillation which were imperfectly controlled by quinidine sulphate. Oxygen was administered continuously by nasal catheter. This situation persisted for several weeks.

In the intervals between the episodes of auricular fibrillation the patient's pulse was rapid, thready, and showed many runs of premature contractions. The blood pressure remained at 90 mm. Hg systolic and 50 mm. diastolic except for several occasions when the systolic level fell below 80 mm. About 10 weeks after the onset a gradual improvement was noted. The episodes of auricular fibrillation became shorter in duration and occurred less frequently. The systolic blood pressure approached a level of 100 mm. Hg and, with the attending gain in strength, the oxygen was no longer necessary. The pulse, between the episodes of fibrillation, became slower, more regular and more forceful.

At this time the patient began to complain of pain in both shoulders, both hands and both knees. Some stiffness of the fingers and hands was also noted. During the next six weeks thickening of the palmar surfaces of both hands developed. The pain diminished but the stiffness persisted. The changes in the palmar fasciae progressed slowly during the next four or five months until definite contractures were present. The pain in the shoulders was not constant but recurred several times. At no time was swelling, redness or lividity of the hands noted. A visible and palpable ridge, extending from the thumb into the palm formed in both hands, being more marked in the left palm. The skin of the entire palm became thickened and hardened bilaterally. The condition has been stationary during the past two or three months. Pain and stiffness in the knees recurred at times but diminished in severity. No plantar changes were observed.

The patient subsequently improved clinically. The blood pressure rose to 120 mm. Hg systolic and 70 mm. diastolic and fibrillation had not occurred, although occasional premature contractions were noted. When last seen, seven months after the onset, she was able to be up and about for short intervals. She was asymptomatic except for some stiffness in fingers and hands.

An electrocardiogram of December 14, 1941, showed regular sinus rhythm with a rate of 76 per minute. QRS voltage had increased in Leads I and II. ST_1 and T_1 were isoelectric. ST_2 was slightly depressed with T_2 erect. ST_3 was slightly depressed with T_3 erect. ST_4 was isoelectric. T_4 was inverted and of low voltage. QRS_4 was monophasic and erect.

DISCUSSION

The changes in the palmar fasciae, closely resembling Dupuytren's contractures, and the coronary vascular accident bear a definite relation to each other. Changes in the palms had not been noted in any instance before the onset of the cardiac difficulty. The coronary occlusion, therefore, ap-

parently acts in some obscure manner as the precipitating factor.   In the cases presented Dupuytren's contracture appears to be a complication of or a sequel to coronary occlusion, as well as the shoulder disability described by several authors,[2,3,4] and the hand syndrome as noted by Askey.[1]

The palmar changes, as noted in the cases here presented, appear typical of Dupuytren's contracture.   The first finding is ordinarily a firm nodule in the palmar aponeurosis, most often in the ulnar area near the metacarpophalangeal joint.   The process is slowly progressive, gradually extending to involve the entire palmar fascia but allowing the tendons to escape.   Due to the fibrosis and contracture of the underlying fascia and to the loss of subcutaneous fat the skin appears thickened, folded, hard and closely adherent.   Although the contracture does not appear in both hands simultaneously, it frequently becomes bilateral.   The typical course is slow but

FIG. 1.

continuous and in the advanced stage results in permanent flexion of one or more fingers to a variable degree.   Although there is an early limitation of extension further voluntary flexion is not limited or painful (figure 1).

Of the 21 cases showing the painful hand syndrome described by Askey,[1] seven showed changes in the palmar fasciae which resembled the early stage of Dupuytren's contracture.   In these cases, however, the process failed to progress to the stage of contracture and a regression was noted in two cases. In none of the six additional cases here reported has there been any evidence of regression of the palmar changes.   Moreover, in three cases (cases 1, 3, and 6) definite contractures have developed, and in each case the contractures appeared bilaterally.   Although death limited the period of observation in two of the cases, the lesions have been slowly progressive with only one exception.   In case 6, after going on to ridge formation and early contracture, the process has become stationary.

In five instances other symptoms and objective findings referable to the hands were noted (table 1). Pain, stiffness, swelling, livid discoloration, numbness, tingling, and coldness were observed. Stiffness, which was the most common finding, was complained of in four instances. Pain occurred in three cases and was associated with stiffness whenever found. Bluish discoloration, numbness and tingling were each found in three cases. Swelling was noted in two cases but no history of redness could be obtained nor was redness observed. Coldness of the hands was found only once. The color changes and associated paresthesias bear out Askey's statement

TABLE I

Case	Occupa-tion	Shoulder Disability	Time of Onset	Objective and Subjective Changes in Hands	Rheumatic History	Arterio-sclerosis	Course
P. H. 48 yrs.	laborer	severe bi-lateral	3 mos. after oc-clusion	marked bilateral contrac-tures; pain, stiffness, numb-ness, tingling, discoloration, and coldness	migratory joint pains 18 yrs.	marked as shown in physical examina-tion	progressive to ad-vanced stage
T. B. 40 yrs.	advertising executive	severe bi-lateral	11 mos. after oc-clusion	small nodule, right hand only, discoloration, numbness, and tingling	none	none	slowly pro-gressive
T. C. 46 yrs.	real estate salesman	none	uncertain	bilateral contractures; pain, swelling, stiffness, and dis-coloration	none	marked general-ized as shown in autopsy	progressive until time of death
N. J. 60 yrs.	retired ex-ecutive	none	uncertain	bilateral nodules, no contrac-tures	inflamma-tory rheu-matism 46 yrs.	commen-surate with age	short period of observa-tion
F. J. 59 yrs.	mechanic	bilateral	5 mos. after oc-clusion	bilateral nodules, no contrac-tures; stiffness, numbness, and swelling	painful swollen ankles at 28 yrs.	commen-surate with age	slowly pro-gressive
R. S. 70 yrs.	housewife	bilateral recurrent	4 mos. after oc-clusion	bilateral contractures; pain, stiffness, and thickening over entire palm	none	none	stationary, no regres-sion

that the sympathetic nerves may well play a predominant rôle in this con-dition.

The relation of the time of the coronary incident to the onset of the palmar changes was variable. In two cases it could not be determined accurately, but in the remaining cases it varied from three to 11 months, being three, four, five, and 11 months in the known instances.

Although all of Askey's cases with palmar changes demonstrated the painful shoulder and hand syndrome, two of the cases here presented gave no history of shoulder disability and no objective or subjective hand findings were noted in one. However, one case which gave no history of shoulder complaints did suffer from pain, swelling and stiffness of the fingers. No cases of unilateral shoulder pain were observed. In addition to the pain and stiffness in the shoulders and hands, one patient complained of pain in the knees. There has been no evidence of plantar changes in this case to date.

Although the onset of the Dupuytren's contracture did not occur at the same time in both hands, the lesion became bilateral during the period of observation in five instances. One patient who experienced a long disability in both shoulders developed palmar changes in the left hand only.

In this small series there appears to be little to support the etiological relationship of Dupuytren's contracture to either acute or chronic trauma of the palmar aponeurosis as suggested by some.[5] No history was obtained in any case to support the theory of an hereditary factor.[6] In three instances the occupation was such as to eliminate the consideration of trauma as an etiological factor. In the remaining three cases, those of the laborer, the mechanic, and the housewife, in spite of any possible exposure to trauma, the palmar aponeurosis showed no evidence of thickening until after the coronary thrombosis.

Whether the extensive generalized arteriosclerosis found in one case at necropsy and in another case at physical examination is of significance is impossible to determine in the light of the present incomplete knowledge. It is also to be noted that three patients gave histories of joint pains at an earlier age. The details of these rheumatic episodes are not as complete as could be desired but in two instances acute rheumatic fever is suggested. Whether this is significant is problematical and can be determined only by further observation.

In 1929 Nippert[7] advanced the theory that Dupuytren's contracture developed on the basis of an increase in sympathetic tone. More recently Hale Powers[8] has explained the palmar phenomenon on the basis of irritation and hyperexcitability of the sympathetics due to visceral disease which he indicates is frequently intrathoracic. He placed Dupuytren's contracture in the same category as pulmonary hypertrophic osteoarthropathy, scleroderma and other trophic disturbances. The mechanism by which visceral disease precipitates dystrophies at the periphery is thought to be through irritation of the sympathetic ganglia. Powers also called attention to the association of Raynaud's disease and Dupuytren's contracture. As an explanation of the usual localization of the palmar changes in the ulnar area, he points out that the ulnar nerve bears a more intimate relation to the intrathoracic sympathetic ganglia than the other nerves of the brachial plexus.

Although the mechanism cannot be explained with certainty, the sympathetic nervous system appears to play a part as evidenced by the associated paresthesias and color changes.

SUMMARY

1. Six cases of Dupuytren's contracture as a sequel of coronary occlusion are presented.

2. Dupuytren's contracture may be associated with the syndrome of shoulder disability and painful hands following myocardial infarction.

3. The palmar changes in the cases presented appear to be typical of Dupuytren's contracture in its various stages.

4. Three cases progressed to the stage of contracture and in no case was regression noted.

5. Pain, stiffness, swelling, livid discoloration, numbness, tingling, and abnormal skin temperature of the hands may be associated with the palmar changes.

6. The etiology and pathogenesis are not understood, but irritation of the sympathetic ganglia may play an important etiological rôle.

I wish to thank Dr. G. C. Owen, Oshkosh, Wisconsin, for the privilege of including case 6, in this series.

BIBLIOGRAPHY

1. Askey, J. M.: The syndrome of painful disability of the shoulder and hand complicating coronary occlusion, Am. Heart Jr., 1941, xx, 1–12.

2. Edeiken, J., and Wolferth, C. C.: Persistent pain in shoulder region following myocardial infarction, Am. Jr. Med. Sci., 1936, cxci, 201.

3. Ernstene, A. C.: Shoulder pain as a sequel to myocardial infarction, Arch. Int. Med., 1940, lxvi, 800.

4. Boas, E. P., and Levy, H.: Extracardiac determination of site and radiation of pain in angina pectoris with special reference to shoulder pain, Am. Heart Jr., 1937, xiv, 540–553.

5. Niederlan, W.: Dupuytren's contraction as related to occupation, Med. Welt, 1933, vii, 126–127.

6. Schroder, C. H.: Dupuytren's contraction and trauma, Arch. f. Orthopäd. u. Unfall-Chir., 1934–1935, xxxv, 125.

7. Nippert: Constitution, metabolism, and Dupuytren's contracture, Deutsch. Ztschr. f. Chir., Leipzig, 1929, ccxvi, 289–292.

8. Powers, H.: Dupuytren's contracture 100 years after Dupuytren: its interpretation, Jr. Nerv. and Ment. Dis., 1934, lxxx, 386–409.

CARDIOVASCULAR SYPHILIS: AN APPROACH TO EARLY CLINICAL RECOGNITION AND EARLY TREATMENT *

By Morris Dressler, M.D., and Moses Silverman, M.D.,
Brooklyn, New York

The aim of the syphilologist and the clinician is to prevent cardiovascular syphilis by early and adequate treatment of the primary infection; the aim of the syphilologist, the cardiologist, and the clinician is to recognize and treat cardiovascular syphilis in its earliest form and as early as possible, in order to prevent the complications that may arise therefrom. Although the former depends primarily on the education of the patient who must seek early treatment and avoid delinquency of treatment, the latter depends primarily on the education of the physician who must be alert to the recognition of this condition.

Syphilis ranks fourth as the cause of cardiovascular disease, following arteriosclerosis, hypertension, and rheumatic fever. Heart disease due to syphilis is the only one whose etiologic agent is definitely known and for which preventive measures are not only known but are available. According to Blumgart,[1] cardiovascular syphilis is responsible for more adult deaths than is neurosyphilis, and constitutes 10 to 15 per cent of all cardiovascular disease. Approximately 5 per cent of all patients who come to autopsy in general hospitals show evidence of cardiovascular syphilis,[2] and of all patients with syphilis, 55 to 86 per cent show syphilitic involvement of the cardiovascular apparatus as revealed at autopsy.[3] One third of the sudden deaths due to heart disease are the result of cardiovascular syphilis.

Leiby, Callaway, and Fleming[4] state that it has been estimated that between 30,000 and 40,000 deaths occur annually from cardiovascular syphilis. According to them, the life expectancy of patients with cardiovascular syphilis ranges from one to 10 years among patients with extensive involvement of the aorta to that of a normal lifetime for those with uncomplicated syphilitic aortitis who receive adequate treatment.

Of all the diseases of the cardiovascular system, uncomplicated syphilitic aortitis is the most frequently overlooked, and yet it is the most common form of visceral syphilis (70 per cent).[5] This may be due to a silent phase of the disease which no doubt depends upon the extent and distribution of the pathologic process, and a clinical diagnosis is, therefore, impossible. However, a more important reason for this oversight is probably the inability of the physician to evaluate the early clinical signs, and to bear in mind the possibility of this condition.

PURPOSE

This study was undertaken for two reasons: (1) because of the confusion existing in the current literature concerning the difficulty or impossibility of making a clinical diagnosis of uncomplicated syphilitic aortitis, and (2) to evolve a method of early clinical recognition if possible.

According to White and Wise,[6] a clinical diagnosis of aortic syphilis can rarely be made within 10 years after infection, and therefore the early diagnosis of cardiovascular syphilis is impossible. Cabot and Adams[7] claim that syphilis of the aorta cannot be recognized clinically unless there is an appreciable degree of aortic valve involvement or considerable dilatation of the aorta with or without actual aneurysm. Garvin[8] believes that uncomplicated syphilitic aortitis is a disease virtually without symptoms or signs. According to the criteria of the New York Heart Association,[9] uncomplicated syphilitic aortitis frequently escapes clinical recognition since it seldom produces symptoms, but evidences of its presence may be found within three to 10 years after the chancre.

The prerequisites for this study are (1) to examine patients with proved syphilis, (2) to examine a large series of patients, (3) to have a single examiner see these patients, and (4) to corroborate the clinical diagnosis by instrumental methods, by follow-up study to discover complications, and by postmortem examination. All these prerequisites were fulfilled in this study with the exception of postmortem examinations, because these cases were followed in a large social hygiene clinic of the New York City Health Department where there are no hospital facilities.

MATERIAL AND METHOD OF STUDY

This paper is a preliminary report of the study of 1270 cases of proved syphilis over a period of two years. In a subsequent paper we will be able to give more detailed data on the follow-up study to discover complications, and add more cases to our series.

All patients were examined by one of us (M.D.). No attempt was made to select the cases. They were referred for cardiovascular check up for the following reasons: (1) prior to starting arsenic therapy in latent asymptomatic cases, (2) because of the advanced age of the patient, (3) as a newly admitted case, (4) because of complaints referable to the cardiovascular system (very few), and (5) as a case of congenital syphilis.

The routine history consisted of the following questions: (1) dyspnea on exertion (great emphasis was placed on evaluating this symptom correctly); (2) paroxysmal nocturnal dyspnea; (3) precordial or substernal pain (pain in other areas (as the spine) was investigated); (4) ankle or leg edema (peripheral vascular and orthopedic conditions were ruled out); (5) cough or hemoptysis; (6) dysphagia; (7) dysphonia; (8) other etiologic factors were sought for (rheumatic fever, hypertension, etc.).

The routine physical examination consisted of the study of (1) the pulse and blood pressure in both upper extremities; (2) the peripheral and neck vessels, including the suprasternal (episternal) notch; (3) the chest wall for pulsations, thrills, or deformities; (4) the size of the heart and aorta by percussion; (5) the auscultatory signs of the anterior and posterior chest (heart and lungs), including the mitral, pulmonic, and aortic areas, with emphasis on the character of the sounds, the intensity of the sounds, and the presence or absence of murmurs. When the base of the heart was examined, the patient was placed in the erect sitting position (bending slightly forward) and auscultation was performed in forced expiration.

Fluoroscopy and roentgenography were used only under the following conditions, and not as a routine in all the cases of syphilis examined: (1) a definite clinical diagnosis of uncomplicated aortitis; (2) the presence of the complications of cardiovascular syphilis; (3) the suspicion of the presence of cardiovascular syphilis; (4) if hypertension or other diseases of the heart were present.

In a preliminary examination of a certain number of cases of proved uncomplicated aortitis and aortic insufficiency, it was noted that the aortic second sound was heard best in many instances over the third right intercostal space near the sternum and in some cases over the fourth right intercostal space, and not as anticipated over the conventional second right intercostal space. Furthermore, it was also noted that in some cases a systolic murmur (as well as a diastolic murmur) was heard best over the third left intercostal space near the sternum, and at times was only heard over this area. In most cases the systolic murmur was heard over the second, third, or fourth right sternal space or in more than one of these areas. This proved that in many instances the change in the character of the aortic second sound, as well as murmurs, may be overlooked if examination of these areas is omitted, thereby missing the clinical diagnosis of uncomplicated aortitis. Another point of interest in physical diagnosis was the importance of comparing the character of the aortic second sound with that of the pulmonic second sound as well as the intensity of these sounds.

According to the criteria of the New York Heart Association,[9] hypertension is present when the systolic blood pressure is persistently above 140 mm. Hg or the diastolic above 90 mm. Hg. In order to avoid any question of borderline cases, hypertension was considered present in this study with a systolic pressure above 150 mm. Hg or a diastolic above 100 mm. Hg.

The cases found to show evidence of uncomplicated aortitis were divided into two groups: those 40 years of age or younger, and those over 40 years, because in the latter group arteriosclerosis cannot be excluded, and one cannot be certain whether dilatation of the aorta is due to aortitis, arteriosclerosis or a combination of both. Aortic sclerosis may also give rise to the characteristic aortic second sound which cannot be differentiated from that of aortitis.

RESULTS

Of the 1270 cases of syphilis examined, 304 (24 per cent) were diagnosed clinically as uncomplicated syphilitic aortitis, and 390 (30.7 per cent) constituted the entire group of cardiovascular syphilis. Among the 390 cases, there were 304 (78 per cent) cases of uncomplicated aortitis, 37 (9 per cent) cases of aortic insufficiency, 19 (5 per cent) cases of aortic insufficiency plus aneurysm, and 4 (1 per cent) cases of coronary ostial stenosis. There were 245 (63 per cent) male patients, 145 (37 per cent) female patients, 255 (65 per cent) white patients, and 135 (35 per cent) negro patients. In other words the proportion of males to females was approximately 2:1, and that of the white to the negro race approximately the same.

Table 1 shows the admission diagnosis of the 390 cases of cardiovascular syphilis. It will be noted that only 72 cases exhibited evidence of cardio-

TABLE I

Analysis of Admission Diagnosis of 390 Cases of Cardiovascular Syphilis

Admission Diagnosis	Number of Cases	%
Primary	3	0.7
Secondary	9	2.4
Early Latent (asymptomatic)	21	5.5
Late Latent (asymptomatic)	240	61.5
Central Nervous System	32	8.2
Cardiovascular	72	18.5
Congenital	8	2.0
Gumma of Bone	3	0.7
Tertiary Skin	2	0.5
Total	390	100.0

vascular syphilis on admission. The other 318 cases developed their cardiac lesions while under observation.

In analyzing the 304 cases of uncomplicated aortitis by decades, 275 (90.4 per cent) occurred between the ages of 21 and 60, and the cases were just as frequent in the third decade as in the fifth. In the age group 40 years or younger, there were 148 (48.7 per cent) cases, and in the group over 40 years, there were 156 (51.3 per cent) cases (table 2). Levitt and Levy [10] in their study of 508 cases of syphilitic aortic disease found that 78.8 per cent of the total number occurred between 31 and 60 years of age.

In further analyzing this group of 304 cases, the proportion of males to females is approximately 2:1. The Coöperative Clinic reports syphilitic aortic disease three times more common in the male than in the female. Other clinics report as high as 5:1. Uncomplicated aortitis is proportionately twice as common in the negro race as in the white in the group 40 years of age or younger, and more common in the negress than in the others (male negro, male and female white). In the older group the white male predominates followed in order by the white female, negro male and negress

TABLE II

Analysis of 304 Cases of Uncomplicated Syphilitic Aortitis by Decades

Age	Number of Cases	%
1–10	0	0.0
11–20	6	2.0
21–30	73	24.0
31–40	69	22.7
41–50	73	24.0
51–60	60	19.7
61–70	21	7.0
71–80	2	0.6
Total	304	100.0

(table 3). Musser[11] observes that central nervous system manifestations are less likely to occur among the negro race than are the cardiovascular, and that, therefore, the vasotropic strain of spirochete would be more prevalent among this race than the neurotropic. According to Turnville[2] cardiovascular syphilis is two to three times more prevalent among negroes than among whites, and he explains this by the prevalence of syphilis among negroes, lack of adequate treatment and the fact that they are more apt to do heavy manual labor. We believe that the negro acquires his syphilis earlier in life than the white and that this accounts for the prevalence of cardiovascular syphilis, especially in the younger age group.

TABLE III

Uncomplicated Aortitis in Relation to Age Group, Sex, and Race

Age Group	Total No. Cases—304				White—182 (59.8%)				Negro—122 (40.2%)				Total	%
	Male		Female		Male		Female		Male		Female			
	Cases	%	Cases	%	Cases	%	Cases	%	Cases	%	Cases	%		
40 yrs. or Younger.....	82	27.0	66	21.7	42	23.1	24	13.2	40	32.7	42	34.5	148	48.7
Over 40.......	108	35.5	48	15.8	86	47.3	30	16.4	22	18.1	18	14.7	156	51.3
Total.....	190	62.5	114	37.5	128	70.4	54	29.6	62	50.8	60	49.2	304	100.0

Neurosyphilis was present in 104 (26.6 per cent) of the 390 cases of cardiovascular syphilis with males predominating over females two to one, and whites over negroes five to one. The frequency of central nervous system syphilis in cardiovascular syphilis is given as 10 per cent by Riven and Feigenbaum[12] and as 16–20 per cent by White.[13]

Relative to the history of the primary infection, 128 (32.8 per cent) of the 390 cases of cardiovascular syphilis remembered the chancre, whereas 262 (67.2 per cent) gave a negative history. Of those who remembered the chancre, uncomplicated aortitis was diagnosed within 10 years after the primary infection in 38 cases, of which 24 were negroes and 14 were white

patients. They were classified as follows in the order of years after the chancre: first year—one case; second year—three cases; third year—three cases; fourth year—three cases; fifth year—five cases; sixth year—three cases; seventh year—six cases; eighth year—five cases; ninth year—four cases; tenth year—five cases.

A study of the relationship between hypertension and cardiovascular syphilis showed that 185 (47.4 per cent) of the 390 cases of cardiovascular syphilis had hypertension. Among the 304 cases of uncomplicated aortitis there were 134 cases (44 per cent) of hypertension (table 4). In order to determine whether these figures were coincidental, the balance of the 1270 syphilitics or 880 cases was used as a control group. Among this group there were cases without cardiac disease, with arteriosclerotic heart disease,

TABLE IV

Analysis of Number of Cases of Hypertension Among 390 Cases of Cardiovascular Syphilis

Race	Sex	Uncompl. Aortitis	Aortic Insuff.	Aortic Insuff. plus Aneurysm	Aneurysm	Cor. Ost. Stenosis	Total
White.....................	M	59	12	0	10	2	83
	F	27	9	1	2	1	40
Negro....................	M	19	2	2	1	0	24
	F	29	5	0	4	0	38
Total........................		134	28	3	17	3	185

hypertensive heart disease, rheumatic heart disease, and congenital heart disease. Hypertension was present in 100 cases (11.3 per cent). In other words, in this large series of syphilitics, hypertension was four times as common among those with cardiovascular syphilis as among the cases without cardiovascular syphilis. To determine further whether this was a coincidental finding and depended entirely upon the presence of hypertension in the older age group, it was found that 50 cases (27 per cent) occurred in the group 40 years or younger. Of this number, 18 (29.1 per cent) were negresses, 12 (19.3 per cent) were male negroes, 11 (8.9 per cent) were white males, and nine (7.4 per cent) were white females. Although hypertension is quite a common finding among negroes, in the older age group the whites overshadowed the negroes by 103 cases (76.3 per cent) to 32 cases (23.7 per cent), a proportion of over three to one, even though the proportion of whites to negroes in the entire group of cardiovascular syphilis was less than two to one (table 5). This proved that the large percentage of hypertension did not depend solely upon the negroes.

There were 50 cases of congenital syphilis among the 1270 cases of syphilis examined. Of these, eight cases (16 per cent) showed definite clinical evidence of uncomplicated aortitis. The ages of the positive cases varied between 13 and 40 years with an average of 20 years. All but one showed evidence of varying degrees of dilatation of the ascending aorta by

fluoroscopy and roentgenography. Coincidently there were four cases of congenital heart disease among the 50 congenital syphilitics. Among the eight cases of congenital cardiovascular syphilis, there were two cases (25 per cent) of neurosyphilis.

Of the 304 cases of uncomplicated aortitis, five (1.6 per cent) showed no evidence of a dilated aorta by fluoroscopy and roentgenography, and one of these had congenital syphilis. The clinical diagnosis of aortitis was unmistakable in this group.

There were 12 cases (with ages ranging between 48 and 55 years) that showed clinical evidence of hypertensive-arteriosclerotic heart disease. When examined by fluoroscopy and roentgenography, each showed the presence of an aneurysm. These cases were not included in our series but are mentioned

TABLE V

Hypertension in Relation to Age Group, Race, and Sex

Age Group	White—123 (66.5%)				Negro—62 (33.5%)				Total	%
	Male		Female		Male		Female			
	Cases	%	Cases	%	Cases	%	Cases	%		
40 yrs. or Younger	11	8.9	9	7.4	12	19.3	18	29.1	50	27
Over 40..............	72	58.5	31	25.2	12	19.3	20	32.3	135	73
Total.............	83	67.4	40	32.6	24	38.6	38	61.4	185	100

to demonstrate the value of instrumental means in making a diagnosis of cardiovascular syphilis.

There were nine cases of rheumatic heart disease and one case of congenital heart disease associated with cardiovascular syphilis in this series. The congenital case was most interesting and unique in that it was one of dextrocardia with complete situs inversus in a woman 43 years of age. The diagnosis of uncomplicated aortitis and congenital heart disease was made clinically and verified by instrumental means.

All cases of complicated cardiovascular syphilis presented one or more symptoms with the exception that most of the early and moderately advanced aneurysms were symptomless. None of the cases of uncomplicated aortitis presented any symptoms unless they were associated with other types of heart disease (hypertensive, functional heart disease, etc.).

Of the 390 cases of cardiovascular syphilis, 12 (3 per cent) received early adequate treatment, 20 (5 per cent) received late adequate treatment, and 90 (23 per cent) were delinquent in treatment at one time or another.

DISCUSSION

Moore and Metildi [14] define uncomplicated syphilitic aortitis as a diffuse supravalvular involvement of the aortic wall, with or without dilatation, but

without valvular incompetency or saccular aneurysm. It is obvious from this definition that uncomplicated syphilitic aortitis may be present without a dilated aorta. According to White and Wise,[6] the first few centimeters of the aorta are commonly first affected by syphilis, and dilatation of this portion, unless extreme, cannot be made out, even by roentgenographic examination, because it is located in the midst of the base of the heart. Maynard[15] reports that of 20 autopsied cases of syphilis, two of three who were thought to have normal aortas showed no disease whereas the third showed syphilitic aortitis, and he comments that to make the diagnosis of uncomplicated aortitis, dilatation of the aorta must be established beyond reasonable doubt. It appears, therefore, from this report that aortitis may be present in a normal sized aorta but to make a diagnosis (by fluoroscopy or roentgenography) the aorta must be dilated.

Is a clinical diagnosis of uncomplicated aortitis impossible in the presence of a normal sized aorta? From our observations we believe that such a diagnosis is possible, and have, therefore, established the following criteria for clinical diagnosis in patients 40 years of age or younger:

(1) The presence of a characteristic aortic second sound. This sound may be described as tambour, drum-like, tympanitic, or hollow, and is usually heard over the second or third right sternal space, and sometimes over the fourth space.

(2) The presence of a systolic murmur over the aortic area (second, third, or fourth right sternal space, over the sternum, the third left sternal space, or in more than one of these areas). A systolic murmur has been heard in many instances over the mitral area.

(3) The presence of suprasternal (episternal) pulsations. This sign indicates elongation and dilatation of the aortic arch.

(4) The presence of increased retromanubrial dullness in the second intercostal space. This sign is of value only when the aortitis is far advanced, and there is moderate or marked widening of the aorta.

(5) The presence of hypertension as a diagnostic aid. Both systolic and diastolic pressures are elevated.

(6) Corroboration of the clinical findings by the use of fluoroscopy and roentgenography to demonstrate the presence or absence of a widened aorta.

According to Carter and Baker,[16] the presence of the characteristic aortic second sound at the aortic area means definite structural change at the aortic ring or at the very origin of the ascending arch or both. This change in tone does not depend upon blood pressure increase. Parsonnet and Bernstein[17] claim that the presence of a bell-like or tambour quality second aortic sound in an individual of 30 or thereabouts may be regarded as almost pathognomonic of uncomplicated syphilitic aortitis. Musser[11] believes that the most valuable physical finding, in fact any finding objective in nature, is the characteristic second aortic sound in the diagnosis of syphilitic aortitis.

The fact that the characteristic aortic second sound is often heard at the

third right sternal space and sometimes at the fourth right sternal space indicates a change in the normal topography of the aorta and heart. According to Dressler,[18] changes in one section of the heart exert an effect on the shape and topography of adjacent portions, displacing them from their normal position and distorting their contours. It is our opinion, therefore, that as the aorta dilates and elongates, the anatomic position of the aortic valve is altered, thereby causing the transmission of sound to areas other than the conventional aortic area.

It is admitted that recognition of the characteristic second aortic sound requires an experienced ear just as Dressler and Moskowitz[19] have demonstrated that in obstetrics auscultation requires acuity of hearing at low frequencies, since in certain cases the ear is incapable of detecting fetal heart sounds. Nevertheless, if one is alert to this condition, experience will come with the recognition of individual cases.

The presence of hyperthyroidism or any condition that can cause a tachycardia may produce the characteristic aortic second sound as well as a systolic murmur. This is due to the increased stroke volume which will increase the velocity of the blood at the semilunar valve orifices, thereby producing alteration in the acoustic qualities. Under such conditions both the aortic and pulmonic second sounds have the same quality, and by comparing these sounds aortitis will be ruled out.

The systolic murmur which occurs with any degree of dilatation (slight, moderate, or marked) at the aortic area is due to the fact that the blood leaving the left ventricle in systole enters a wider chamber and sets up abnormal vibrations. In other words there is an ejection of the blood column during systole through the normally constricted aortic ring into an abnormally dilated aorta. Leiby, Callaway, and Fleming[4] believe that the systolic murmur of an early aortitis may be due to a roughened intima, a dilated aorta with changes in the sounding structure, or a combination of these.

In the beginning the systolic murmur is soft and is usually not transmitted. Later in the disease the murmur becomes rough and harsh and is transmitted into the vessels of the neck, and down along the left sternal border. Occasionally the murmur may be heard at the apex, and we believe that it is transmitted from the aortic area. According to Sprague,[20] murmurs, in the main, are transmitted best in the direction of the current. This is due to the fact that the eddies are propagated and released in this direction, but more to the fact that the point of impact of the stream upon a solid body must be distal to the obstruction. However, if the murmur is loud enough, it will be transmitted somewhat in all directions by local resonators and direct continuity of solid bodies.

When pulsations are felt in the suprasternal notch, this valuable sign indicates the presence of a dilated and elongated aorta. Stern[21] believes that since the first portion of the aorta is held firmly by the heart, which is anchored by the pericardial sac, and the descending portion is attached to the spine, any lengthening must be accompanied by a bulging upward of the

arch. This elevation pushes up the origin of the vessels that arise from the arch and causes them to bend and buckle. This buckling places a portion of the artery (especially the innominate or right carotid) into the suprasternal notch where it can be felt and at times seen. The impulse under these circumstances comes chiefly from the right and may be mistaken for an aneurysm of these vessels. If the finger is inserted deeply into the suprasternal notch, the aorta itself can be felt as a horizontal pulsating vessel and a diagnosis of an elongated and dilated aorta is easily made. The dilated aorta may cause pulsation in the second or third right or left intercostal spaces which is often mistaken for an aneurysm.

Increased retromanubrial dullness is valuable as a sign only when the aortitis is far advanced and there is moderate or marked widening of the aorta. According to Leaman,[22] if the aorta is inspected in the cadaver, it will be seen to arch in a direction away from the chest wall. In addition, the vessels at the base of the heart are surrounded by lung tissue. Therefore, it is difficult to indicate the diameters of the aorta with any degree of accuracy by percussion over the anterior chest wall. We believe that other conditions such as a deformed anterior chest wall, a thickened chest wall, and emphysema may interfere with accurate percussion in spite of the size of the aorta.

The question of the association of hypertension with cardiovascular syphilis has been a controversial one. Moore, Danglade, and Reisinger[23] studied 105 patients with uncomplicated aortitis who came to necropsy and found that hypertension was an infrequent accompaniment of this condition. Horine and Weiss[24] studied 666 patients with essential hypertension and a control group of 2000 non-hypertensive patients and concluded that syphilis was practically the same in both groups and that, therefore, it cannot have any etiological bearing on hypertension. We believe that our study was more representative because both the group with cardiovascular syphilis and the control group were cases of proved syphilis. On the other hand, Scherf and Boyd[5] state that about 50 per cent of the cases of aortitis have an increased blood pressure (over 150 mm. Hg) which affects the systolic as well as the diastolic pressures. Nothing is known about the cause of this hypertension, and they believe that perhaps factors other than an extension of the inflammatory process to the depressor nerve in the aortic wall are responsible. From our studies it is obvious that hypertension is a common finding in syphilitic aortitis and can be used as a diagnostic aid because the very frequent combination of these two conditions makes it obligatory to consider the possibility of aortitis in every hypertensive patient, especially when the hereditary factor in hypertension can be ruled out from the family history.

Another disputable question has been that of the rôle of hypertension in causing the characteristic aortic second sound. Gager[25] believes that a drum-like or booming quality of the aortic second sound is the result of hypertension. On the other hand, Carter and Baker[16] believe that accentuation of the aortic second sound indicates high pressure levels, whereas a

change in quality means structural alteration in the cusps, ring, or vessel. According to Best and Taylor,[26] the second aortic sound results from the vibrations set up in the blood column and arterial wall as the aortic valve is placed under tension following its closure. The intensity of the second aortic sound is increased by an elevation in the systemic pressure. The condition associated with intensification of the second aortic sound is hypertensive disease which raises the aortic pressure. We believe that hypertension can cause a change in the character of the second sound at the aortic area in addition to accentuation, only when advanced aortic sclerosis is associated with it. Therefore, in the age group of 40 years or older one is unable to differentiate aortitis from aortic sclerosis, with or without the presence of hypertension. Hypertension causes accentuation of the second aortic sound; aortitis and aortic sclerosis change the character of the second aortic sound.

Although this paper deals primarily with the physical diagnosis of uncomplicated syphilitic aortitis, we cannot help but make a few observations on the use of fluoroscopy and roentgenography. It is generally agreed that the use of these instrumental methods requires experience and judgment. There has been much discussion in the literature concerning the value of fluoroscopy and teleoroentgenography in detecting early uncomplicated syphilitic aortitis. Kemp and Cochems [27] conclude from their studies of 1000 unselected syphilitics with those of 600 unselected non-syphilitics, that there is no evidence that the diagnosis of uncomplicated syphilitic aortitis can be made by teleoroentgenography alone; fluoroscopy and careful clinical evaluation of symptoms and physical signs are essential. Blitch, Morgan, and Hillstrom [28] were unable to find roentgenographic and fluoroscopic evidence of syphilitic aortitis among 30 patients with syphilis of 12 years' duration. Padget and Moore,[29] in a critical review of the literature on the roentgenographic diagnosis of uncomplicated syphilitic aortitis, state that commonly used teleoroentgenographic studies were valueless, that the left anterior oblique position might hold some promise, and that fluoroscopic examination in the hands of a competent observer may have some value. Maynard [15] does not place reliance on teleoroentgenography and measurements of the vascular pedicle alone but on careful clinical, fluoroscopic, and orthodiagraphic studies in addition.

In our corroborative studies of the physical diagnosis of uncomplicated aortitis by means of fluoroscopy and roentgenography, we did not use any measurements but depended primarily on our experience in evaluating dilatation of the aorta. We considered age, sex, size, body build, and chest deformities in our evaluation, and found that the left anterior oblique view was most valuable for the study of the aorta.

It will be noted from our results that uncomplicated syphilitic aortitis is a truly asymptomatic disease. Opinions differ on this statement. Cole and Usilton [3] include in their criteria for the diagnosis of uncomplicated aortitis a history of circulatory embarrassment, progressive cardiac failure, substernal pain, and paroxysmal dyspnea. Maynard [15] has aptly shown

that from his experience these findings are the result of the complications of aortitis. Wilson [30] studied 211 patients with syphilitic aortitis and demonstrated that every case with symptoms referable to the heart had one of the complications of cardiovascular syphilis or some coexisting disease. He concluded that uncomplicated syphilitic aortitis was an asymptomatic disease and that no criteria dependent upon symptoms were reliable in making an early diagnosis.

Most text books and periodicals claim that cardiovascular syphilis is rare among congenital syphilitics. Our results show that 16 per cent of the congenital cases studied presented clinical evidence of aortitis, and all but one showed some degree of aortic dilatation by fluoroscopy and roentgenography. Kurtz and Eyster [31] studied a small series of 12 cases of congenital syphilis with special reference to the fluoroscopic findings in the heart and aorta. The fluoroscopic evidence of aortitis was found in 36.4 per cent of the cases. They based the diagnosis of the presence of aortitis and the degree (slight, moderate, or marked) upon the shape of the ascending aorta—sagging of the ascending aorta to the right with pulsations visible to the right of the sternum, and the density of the descending aorta. Cardiovascular syphilis is rare in infants with congenital syphilis, but in older children and adults who have received inadequate or no treatment there is no reason why this condition should not be recognized more frequently, especially since it has been demonstrated that central nervous system syphilis is just as frequent in congenital syphilis as in the acquired type. Kurtz [32] reports a series of 20 cases with congenital syphilis studied by fluoroscopy and orthodiascopy. There were seven males and 13 females ranging from nine to 47 years of age. Most of these had received no antisyphilitic therapy up to the time of admission. The aorta was dilated slightly in seven cases, moderately in one, and appeared normal in the remaining 12. He makes no mention of the physical findings in the eight cases (40 per cent) of aortitis.

All the congenital syphilitics studied were proved cases, and the criteria for the clinical diagnosis of syphilitic aortitis were the same as in the acquired type. Yampolsky and Powel [33] report a case of proved congenital syphilis in a nine year old child in whom the diagnosis of aortitis of syphilitic origin was made pathologically. McDonald [34] reports 11 cases of syphilitic aortitis occurring in patients up to 30 years of age with congenital syphilis. The diagnosis was made post mortem. These cases were not followed for any period of time before death but were admitted to the hospital with various acute conditions. Some degree of coronary ostial stenosis was present in practically all the cases.

TREATMENT

No attempt will be made to present an exhaustive treatise on the treatment of cardiovascular syphilis but rather to point out the dangers and discuss the routine of such treatment.

It should be remembered that in treating patients with cardiovascular syphilis there is a greater tendency to react unfavorably to medication, and the reaction is likely to be more severe and dangerous than in a patient who has no cardiovascular involvement.

In outlining a program for the treatment of cardiovascular syphilis, Moore [35] considers the possibility of reactions and plans his treatment with the idea of prevention.

During treatment or immediately thereafter the patient may suddenly show pallor followed by marked tachycardia, cold perspiration, failing pulse, and occasionally death within a few minutes. This reaction is likely to occur when the drug used is old arsphenamine, and it may be due either to the greater toxic effect of the drug or possibly to the greater volume of fluid necessary for its administration. By the use of milder drugs less toxic in nature, and in smaller easily controlled doses, this reaction can to a certain extent be avoided.

The very common mild nausea and vomiting that occur in certain types of patients after treatment present a danger in cardiovascular syphilis and should be prevented. Here also smaller doses of less toxic drugs are of value in preventing any serious damage to the myocardium.

A complication associated with the treatment of cardiovascular syphilis is the so-called therapeutic paradox. Here we have an apparently healthy patient with a well compensated heart suddenly developing congestive heart failure after a course or two of antisyphilitic therapy. This is explained by the too rapid healing of the inflammatory tissue and its replacement by scar tissue, with the inflammatory process subsiding but the patient in a poorer condition than before treatment was started. This reaction can be avoided by giving a preliminary course of bismuth and iodides followed by small doses of mildly acting arsenicals such as neoarsphenamine or mapharsen.

The Herxheimer reaction which may occur a few hours after the first injection of an arsenical, must be borne in mind and carefully avoided. The local edema in the aorta that comes on suddenly may be particularly dangerous if it occurs at the mouth of a coronary artery, where it may lead to immediate death. This reaction can be avoided by starting with a course of bismuth and iodides followed by very minute doses of the arsenicals.

All patients with cardiovascular syphilis should be started with a preparatory course of bismuth [36] and iodides, before any arsenical therapy is attempted. This course should consist of at least 10 to 12 intramuscular injections of bismuth subsalicylate in oil (0.1–0.2 gm.) at weekly intervals followed by a similar course of neoarsphenamine (0.1 gm.) or mapharsen (0.01 gm.) and gradually increasing the dosage. With the exception of cases with uncomplicated syphilitic aortitis, the dosage should not exceed 0.3 gm. of neoarsphenamine or 0.03 gm. of mapharsen in any cardiac condition. Old arsphenamine should never be used in the treatment of cardiovascular syphilis.

The course of treatment should be continuous without any rest period,

and if there are no reactions or contraindications, it should be continued for at least two years. As a rule the best procedure is to alternate the treatment so that 10 to 12 injections of bismuth are followed by 10 to 12 injections of an arsenical, and repeated until treatment is discontinued. Although the serological reaction may be checked during this period of treatment, this should have no bearing on the length and type of treatment. At the termination of this regime of treatment, if sufficiently improved the patient is given a rest period of six months and asked to return for a cardiovascular check up, and if necessary for a short course of further treatment.

If the patient has developed aortic insufficiency or aneurysm, treatment must be more conservative. Under these circumstances the preliminary bismuth and iodide therapy is started, but the arsenicals must be used with caution and in many instances their use should be avoided. If the administration of arsenicals is attempted, bismarsen 0.1 gm. intramuscularly at weekly intervals may be tried. The treatment here as in uncomplicated aortitis is prolonged, and a minimum period of two years is required before any rest period is permitted. Under no circumstances should a patient with recognized coronary ostial stenosis be treated with an arsenical. If congestive heart failure for any reason occurs, bismuth and arsenic therapy must be stopped.

Finally, it must be remembered that once the inflammatory process has started and progressed to scarring, treatment will have no effect on the terminal result. For this reason if treatment is late, uncomplicated syphilitic aortitis and its complications will be detected while the treatment is in progress. In other words, treatment cannot prevent a pathologic process that has already started and is far advanced, but will stop it at its inception and prevent the occurrence of such a process.

CONCLUSIONS

The successful clinical diagnosis of uncomplicated syphilitic aortitis depends upon the alertness and the ability of the clinician to recognize this condition as well as upon the extent and distribution of the pathologic process. That this condition is frequently overlooked can be readily appreciated from the difference between its incidence in pathological and in clinical reports. In our series the incidence of uncomplicated aortitis is 24 per cent (304 cases) whereas in reported pathological studies the average incidence is 70 per cent. According to these figures it means that in 46 per cent of the cases the pathologic process is too minimal to be recognized clinically, or is so distributed that recognition by physical diagnosis is impossible.

The clinician is confronted with the problem of diagnosing uncomplicated aortitis in individuals 40 years of age or younger with a history of syphilis, without any complaints and with a negative serological test; or with a negative history, no complaints, and a negative serological test; or with a negative history, no complaints, and a positive serological test. It has been

generally estimated that about 20 per cent of the cases of syphilis give a negative serological test. It is this group of patients, with or without a history of syphilis, that requires our attention as well as our diagnostic acumen for the recognition of uncomplicated aortitis, because they are usually met too late, at a time when they have already developed the complications of cardiovascular syphilis.

With this problem in mind, we were able to recognize 148 cases of uncomplicated aortitis in the younger age group. In this group the negro race predominated by approximately two to one. The presence of the characteristic second aortic sound in the various areas designated was by itself diagnostic of this condition. We know of no other cardiac disease in young individuals (except premature arteriosclerosis) that can produce this sound. Tachycardia due to hyperthyroidism or other diseases may produce it, but it can be easily recognized and differentiated. We believe that hypertension per se is not a problem in the recognition of the characteristic second sound, because hypertension can only accentuate this sound. A systolic murmur is commonly associated with the characteristic second sound. The presence of a systolic murmur alone at the aortic area indicates organic heart disease. Willius [37] has aptly made the following assertion, and we quote: "A systolic murmur that is confined to the aortic area is almost without exception indicative of disease of the aorta or aortic valves, namely, aortic stenosis, aortic sclerosis, or aortitis." If in a young individual rheumatic heart disease or arteriosclerosis can be ruled out, a systolic murmur means syphilitic aortitis with or without the characteristic second aortic sound. The other points mentioned under our criteria for physical diagnosis are corroborative.

We wish to emphasize that a clinical diagnosis of uncomplicated aortitis can and should be made in the presence of a normal sized aorta, if definite and unmistakable physical signs are present.

The presence of the large percentage of hypertensives among the cases of cardiovascular syphilis was somewhat confusing because we were unable to give a valid reason for this finding. From a statistical standpoint we were not able to prove that it was merely a coincidental finding. We agreed, therefore, with the conclusions of Scherf and Boyd,[5] and considered hypertension a diagnostic aid.

We believe that uncomplicated aortitis is not an infrequent finding in congenital syphilis, and that if larger series are studied carefully, our results will be corroborated.

The life expectancy of patients who receive early and adequate treatment with uncomplicated syphilitic aortitis is a normal lifetime, whereas with patients who show complicated cardiovascular syphilis, it ranges from about one to 10 years.

SUMMARY

Of 1270 cases of proved syphilis studied, 24 per cent were diagnosed clinically as uncomplicated aortitis, and 30.7 per cent as cardiovascular

syphilis as a whole. Of the latter group, 78 per cent were cases of uncomplicated aortitis. The proportion of males to females was approximately two to one, and that of the white to the negro race approximately the same.

The criteria for the physical diagnosis of uncomplicated aortitis are presented and discussed, and are found of value in patients 40 years of age or younger. It is more common in the negro than in the white race in this age group.

The high percentage (47.4 per cent) of hypertension among the cases of cardiovascular syphilis studied is not purely coincidental. No valid reason is advanced for its presence.

Uncomplicated aortitis is more common among congenital syphilitics than has been reported heretofore.

Of 128 cases of cardiovascular syphilis that remembered the chancre, uncomplicated aortitis was diagnosed in 38 cases within 10 years after the primary infection.

Uncomplicated aortitis is a symptomless disease. Hints on physical diagnosis are discussed.

Neurosyphilis was present in 26.6 per cent of the cases of cardiovascular syphilis.

Fluoroscopy and roentgenography are of value in corroborating the clinical diagnosis. Uncomplicated aortitis can be diagnosed clinically in a normal sized aorta..

An outline of treatment is presented.

BIBLIOGRAPHY

1. BLUMGART, H. L.: Detection and treatment of cardiovascular syphilis, New England Jr. Med., 1940, ccxxiii, 443.
2. TURNVILLE, W. H. H.: Cardiovascular syphilis, U. S. Naval Med. Bull., 1939, xxxvii, 237.
3. COLE, H. N., and USILTON, L. J.: Coöperative clinical studies in the treatment of syphilis: cardiovascular syphilis. Uncomplicated syphilitic aortitis, Ven. Dis. Inform., 1936, xvii, 91. Idem: Arch. Int. Med., 1936, lvii, 893.
4. LEIBY, G. M., CALLAWAY, J. L., and FLEMING, W. L.: Diagnosis and management of asymptomatic uncomplicated aortitis, North Carolina Med. Jr., 1940, i, 301.
5. SCHERF, D., and BOYD, L. J.: Cardiovascular diseases, 1939, C. V. Mosby Company, St. Louis, p. 317.
6. WHITE, P. D., and WISE, N. B.: Early diagnosis of cardiovascular syphilis, New England Jr. Med., 1937, ccxvii, 988.
7. CABOT, R. C., and ADAMS, F. D.: Physical diagnosis, 1938, William Wood and Company, Baltimore, p. 339.
8. GARVIN, C. F.: Incidence and diagnosis of cardiovascular syphilis, Ohio State Med. Jr., 1939, xxxv, 34.
9. New York Heart Association: Nomenclature and criteria for diagnosis of diseases of the heart, 1939, J. J. Little and Ives Company, New York, p. 30.
10. LEVITT, A., and LEVY, D. S.: Syphilitic aortic disease; analysis of 508 cases, New York State Jr. Med., 1940, xl, 648.
11. MUSSER, J. H.: Observations on syphilitic heart disease, Urol. and Cutan. Rev., 1939, xliii, 773.

12. RIVEN, S. S., and FEIGENBAUM, J.: Syphilis of the aorta and heart; a clinical study, Canad. Med. Assoc. Jr., 1930, xxiii, 656.

13. WHITE, P. D.: Diagnosis of cardiovascular syphilis, New England Jr. Med., 1933, cclxviii, 179.

14. MOORE, J. E., and METILDI, P. F.: Uncomplicated syphilitic aortitis: diagnosis, prognosis and treatment, Arch. Int. Med., 1933, lii, 978.

15. MAYNARD, E. P., JR.: Diagnosis of cardiovascular syphilis, Brooklyn Hosp. Jr., 1940, ii, 69.

16. CARTER, E. P., and BAKER, B. M., JR.: Certain aspects of syphilitic cardiac disease, Bull. Johns Hopkins Hosp., 1931, xlviii, 315.

17. PARSONNET, A. E., and BERNSTEIN, A.: Syphilitic aortitis: its early recognition, Urol. and Cutan. Rev., 1940, xliv, 499.

18. DRESSLER, W.: Cardiac topography, Am. Heart Jr., 1940, xix, 141.

19. DRESSLER, M., and MOSKOWITZ, S. N.: Fetal electrocardiography and stethography, Am. Jr. Obst. and Gynec., 1941, xli, 775.

20. SPRAGUE, H. B.: The mechanism of the production of heart murmurs, Part II. Modern Concepts of Cardiovascular Disease, 1937, 6: no. 10.

21. STERN, N. S.: Clinical diagnosis, 1933, The Macmillan Company, New York, p. 160.

22. LEAMAN, W. G.: Management of the cardiac patient, 1940, J. B. Lippincott Company, Philadelphia, p. 12.

23. MOORE, J. E., DANGLADE, J. H., and REISINGER, J. D.: Diagnosis of syphilitic aortitis uncomplicated by aortic regurgitation or aneurysm; comparison of clinical and necropsy observations in 105 patients, Arch. Int. Med., 1932, xlix, 73.

24. HORINE, E. F., and WEISS, M. M.: The relation of syphilis to hypertension; (statistical study), Am. Heart Jr., 1930, vi, 121.

25. GAGER, L. T.: Differentiation of syphilis and hypertension in etiologic diagnosis of heart disease, Med. Bull. Vet. Admin., 1940, xvi, 226.

26. BEST, C. H., and TAYLOR, N. B.: The physiological basis of medical practise, 1939, The Williams and Wilkins Company, Baltimore, p. 286.

27. KEMP, J. E., and COCHEMS, K. D.: Studies in cardiovascular syphilis, Am. Heart Jr., 1937, xiii, 297.

28. BLITCH, C. G., MORGAN, H. J., and HILLSTROM, H. T.: Early (subclinical) aortitis: an evaluation of radiographic diagnostic methods, South. Med. Jr., 1932, xxv, 709.

29. PADGET, P., and MOORE, J. E.: The roentgenologic diagnosis of uncomplicated syphilitic aortitis: a critical review of the literature, Am. Jr. Syph., Gonor. and Ven. Dis., 1937, xxi, 199.

30. WILSON, R., JR.: Studies in syphilitic cardiovascular disease: uncomplicated syphilitic aortitis: asymptomatic condition, Am. Jr. Med. Sci., 1937, cxciv, 178.

31. KURTZ, C. M., and EYSTER, J. A. E.: Fluoroscopic studies of the heart and aorta in acquired and congenital syphilis, Am. Heart Jr., 1930, vi, 67.

32. KURTZ, C. M.: Orthodiascopy, 1937, The Macmillan Company, New York, p. 156.

33. YAMPOLSKY, J., and POWEL, C. C.: Syphilitic aortitis of congenital origin in young children: review of the literature and report of a case, Am. Jr. Dis. Child., 1942, lxiii, 371.

34. McDONALD, S., JR.: Syphilitic aortitis in young adults with special reference to a congenital aetiology, Brit. Jr. Ven. Dis., 1934, x, 183.

35. MOORE, J. E.: Modern treatment of syphilis, 1933, Charles C. Thomas, Springfield.

36. STOKES, J. H.: Modern clinical syphilology, 1934, W. B. Saunders Company, Philadelphia.

37. WILLIUS, F. A.: Cardiac clinics. V. A talk on cardiac murmurs, Proc. Staff Meet. Mayo Clin., 1934, ix, 795.

LIPID METABOLISM IN RELATION TO XANTHOMA DIABETICORUM WITH A RECOMMENDATION FOR A NEW NOMENCLATURE *

By John Garb, M.D., *New York City*

For a clearer understanding of this paper it is thought advisable to give a review of the present conception of fat metabolism with special reference to fat digestion or absorption and some of the essential data on lipids as related to lipid diseases in general and xanthoma diabeticorum in particular. The terms lipid, lipin and lipoid as used today are synonymous, and include the triglycerides of the fatty acids, cholesterol and cholesterol esters, the phospholipins or phosphatides, the cerebrosides, lipochromes and other fat-containing pigments, such as lipofuscin.

Fat Metabolism

It is now the generally accepted view that hydrolysis of the neutral fat of food into its component fatty acids and glycerine is a necessary prerequisite to its absorption. This hydrolysis or splitting of the neutral fat takes place in the small intestine through the actions of the lipase of the intestinal juice —succus entericus—and the pancreatic lipase, steapsin. A certain proportion of the fatty acids, depending upon the reaction of the intestinal contents, form soaps with carbonate and bicarbonate of sodium of the intestinal juices. These soaps, through their property of lowering the surface tension, break up the fat into smaller globules thus forming a finer emulsion of fat with the intestinal juices and thereby increasing the total surface area of the fat exposed to enzyme action.

The bile, aided by cholesterol, plays an essential rôle in the digestion of fat. The bile salts, glycocholate and taurocholate of sodium, help in the saponification of fats. The bile acids dissolve the fatty acids which result from the cleavage of the neutral fat and which are insoluble in the intestinal juices. The bile acids, like the soaps and the fatty acids which are held in solution by the bile acids, likewise have the property of lowering the surface tension of the intestinal juices. They thus further the process of emulsification and increase enormously the surface area of fat exposed to the action of pancreatic lipase. The latter is also specifically activated through the cholic acid radical of the bile salts.

The previously accepted theory proposed by Pflüger[1] that fatty acids are absorbed in the form of soaps according to Best and Taylor[2] is "untenable, for soaps which might be formed could not be held in solution in the acid

fluid of the intestines." Verzar [3] and his colleagues believe that bile acids through hydrotropic action form a complex with the fatty acids (1 molecule of fatty acid to 3 of bile acid) which is soluble and stable in the slightly acid intestinal juices and which diffuses readily into the epithelial cells of the intestinal mucosa. This bile acid-fatty acid complex breaks down into its components after passing the epithelial boundary. The released fatty acids then recombine immediately with the glycerine which has likewise diffused into the cell from the intestinal lumen, and the bile salt is returned through the portal blood stream to the liver. Verzar furnished experimental evidence that as an essential step in the resynthesis of neutral fat in the intestinal mucosa there is an intermediate stage in which phosphorylation of the fatty acid, the introduction of the PO group, occurs with the formation of a specific phospholipid. This observer believes that the adrenal cortex plays an essential rôle in the process of phosphorylation.

The splitting and the resynthesis of the fat in the intestinal mucosa soon after its absorption from the intestinal lumen allow a regrouping of the fatty acid molecules with the formation of a new lipid which is characteristic of each animal species. Bloor [4] has shown that chemical properties of fats are greatly changed in digestion. When an animal is fed with a fat having a high melting point a fat with a lower melting point is recovered in the thoracic lymph, and vice versa. The intestine thus possesses the power to modify the composition of fat during absorption. The new compounds of neutral fats and phospholipids are discharged in a finely emulsified form into the central lymph spaces (lacteals) of the intestinal villi, where the fat appears as a milk-white emulsion called chyle. By rhythmical contractions of the lacteals, the chyle is propelled along into the lymphatics of the mesentery to the receptaculum chyli by way of the left thoracic duct. It then enters the blood stream at the junction of the left subclavian and jugular veins. In the blood the absorbed fats are present in finely emulsified droplets termed chylomicrons.

The blood fat is transported to the tissues, liver and depots for fat. The latter are located mainly under the skin in the superficial fascia or panniculus adiposus, omentum, retroperitoneal regions and interstitial tissue of all organs except in the brain. The fats in the tissues, liver and depots differ in their composition. The storage depots for fat contain almost entirely the triglycerides of the fatty acids which are relatively resistant to oxidation. The fat in the liver is similar in composition to that found in the tissues when active metabolism is not in process and contains much potential energy. During active metabolism the liver fat occupies an intermediary position and is sent to the tissues for utilization. The liver thus seems to act as a storage depot for fat which is ready to be used.

Raab [5] reported a reduction of fat in the blood and tissue and its accumulation in the liver of mammals following pituitrin administration. From this and other experiments he concluded that there is in the anterior and posterior lobes of the pituitary gland, tuber cinereum and walls of the third

ventricle a lipoid influencing hormone which he called lipoitrin and which promotes the absorption and disposal of the blood fat by the liver. Experiments by Bailey and Bremer [6] produced obesity in dogs by a small puncture confined to the hypothalamus in the region of the tuber cinereum. This would point to the hypothalamus rather than the posterior lobe as a factor in the control of fat metabolism.

Schoenheimer and Rittenberg,[7] by feeding mice with fatty acids "earmarked" with deuterium, were able to demonstrate the desaturation of fatty acids in the body. Deuterium is the heavy isotope of hydrogen which can be made to replace ordinary hydrogen in compounds. The concentration of deuterium may be determined accurately in the tissues and the substances isolated from the tissues. With these fatty acid-deuterium compounds they were likewise able to prove that the largest part of the fat in the diet, even when present in small amounts, is first deposited in the depots for fat before it is utilized. The preparation of the fat in the depots for use in the organism may be accomplished easily or with difficulty. In the latter case, it is taken up very slowly and prepared for use very slowly. This shows the advisability of controlling the weight loss of obese patients, so that they do not lose it too rapidly.[8]

The following lipids are found in the serum: Neutral fat, lecithin, cephalin, sphingomyelin, cholesterol and cholesterol esters. The cerebrosides, also called glycolipids or galactolipids, consist of kerasin, phrenosin, nervone and hydroxynervone and are found chiefly in the nervous tissues and in small amounts only in other organs and in the serum. The neutral fats consist of the triglycerides of the fatty acids, palmitic, stearic and oleic which predominate in human fat. Lecithin, cephalin and sphingomyelin comprise the phospholipid group. Lecithin and cephalin are monaminophosphatides in which the ratio of nitrogen to phosphorus is 1 : 1. Sphingomyelin is a diaminophosphatide in which the ratio of nitrogen to phosphorus is 2 : 1. Cholesterol and cholesterol esters and especially sphingomyelin show more constant values in the serum because they depend largely upon the cellular metabolism of organs and tissues and very little upon intestinal absorption.

There is a physiologic increase of neutral fat in the blood plasma after a fatty meal. In an individual at rest one gram of fat per kilogram of body weight is followed by a slow rise in the concentration of blood fat reaching the maximum value in four hours, then rapidly diminishing and returning to the normal level within six to seven hours. In an individual not at rest the rise occurs more rapidly and reaches the maximum within three hours.[9] A permanent hyperlipemia, however, is always the sign of an abnormal metabolic process in the blood. Hyperlipemia is usually recognized by the milky, opaque appearance of the serum; but an increase of fat up to 150 per cent of the normal value may be present without producing a change in the appearance of the serum.[10] Chemical analysis of the serum, therefore, is necessary to determine the presence or absence of hyperlipemia. The

milky appearance of the serum is usually the result of a marked increase in neutral fat and a proportionate increase of lecithin which generally accompanies the neutral fat. An increase in the cholesterol and cholesterol esters does not produce a milky serum. Cholesterol may or may not parallel the increase of neutral fat and lecithin nor are neutral fat and lecithin proportionately elevated with cholesterol.

The milky serum with its extensive increase in neutral fat is characteristic only of secondary xanthomas due to various types of hyperlipemia. In essential xanthomatosis of the hypercholesteremic [11] group the total cholesterol is increased. It is usually accompanied by only a moderate increase of neutral fat, not sufficient to make the serum milky.

The normal figures for serum lipids (Bloor method) as given by the New York Post-Graduate Medical School and Hospital are as follows:

Lipids, total   (500–700 mg. per cent)
    Fatty acids   (200–420 mg. per cent)
    Lipid P (lipid esters of phosphoric acid, or phospholipins which
        include lecithin, cephalin and sphingomyelin)   (7–14 mg. per cent)
Cholesterol, total   (160–230 mg. per cent)
    Cholesterol esters   (100–150 mg. per cent)
    Ratio of esters to total   (40–60 per cent)

Partition of phospholipids (according to the method of Thannhauser, Benotti and Reinstein [12]).

Lipid phosphorus   (8–11 mg. per cent)
Total phospholipid (lecithin, cephalin and sphingomyelin)   (200–290 mg. per cent)
    Sphingomyelin   (15–40 mg. per cent)
    Cephalin   (50–140 mg. per cent)
    Lecithin   (50–200 mg. per cent)

Approximate values for lipoid content of normal skin (epidermis and cutis, excluding the subcutaneous layer) are the following: total lipoids, less than 3 per cent of the wet weight of the tissue (based on immediate analysis of adequately large specimens); total cholesterol, traces to 15 per cent of the total lipoids; and lecithin, traces to 30 per cent of the total lipoids.[13]

The phospholipid values are affected by various hormones. The plasma phospholipids are decreased by insulin whereas they are increased in the liver after repeated injections of thyroid substance. In rapidly growing malignant tumors the phospholipid content of the tumor cells is higher than in benign tumors of the same tissues or in normal tissues.[14]

Lecithins are found in all cells intimately associated with the phenomena of life. They serve in the blood stream as the chief agents for absorption and transportation of fats. Cephalin, which according to Howell [15] is closely related to thromboplastin or thrombokinase, plays an important part in the coagulation of blood.

Cholesterol is a non-saponifiable fat-like body, named cholesterin from the Greek *chole,* bile, and *steros,* solid. It is a monatomic, simple, unsaturated, secondary alcohol belonging to the sterol group, occurring in the human organism free or as esters of palmitic, stearic and oleic acids. Cholesterol is an essential constituent of the body fluids and of all the cells of the

body, the richest supply being in the brain and adrenal cortex. It is synthesized in the body and is absorbed from animal sterols but not to any appreciable extent if at all from plant sterols.[16] Cholesterol occurs in the blood in the free state and as esters. It occurs in the bile as free cholesterol only and mainly in the same form in the brain and in the human blood corpuscles. The concentration of the total cholesterol is normally the same in the plasma as in the whole blood. Bloor and Knudson [16a] found cholesterol esters 33.5 per cent of the total cholesterol in the whole blood and 58 per cent in the plasma, but the ratio may vary in the latter from 40 to 60 per cent. The ratio of free cholesterol to cholesterol esters is 1:1.4. A reversal of this ratio means a decided destruction of the parenchyma of the liver and usually occurs in xanthomatous biliary cirrhosis.[16b]

Cholesterol esters, like the neutral fats, are hydrolized by the intestinal and pancreatic enzymes and are resynthesized in the intestinal mucosa before reaching the lymph stream, by which route they are mainly absorbed, some of it being taken up directly by the blood stream. Rothschild and Felsen [16c] believe that the liver is the regulator of the cholesterol metabolism, maintaining it at a more or less constant level by excreting the free cholesterol only in the bile and intestine. Some of the biliary cholesterol is reabsorbed from the small intestine, another part is destroyed by the colon bacilli (Ottenstein and Nekam [16d]) but the bulk is transformed by hydrogenation * or reduction to coprosterol and with some unchanged cholesterol is eliminated in the feces. Gardner and Kingsborough [16e] state that cholesterol can be found normally in the urine. Rothschild and Felsen [16c] found the cholesterol low in three cases of acute yellow atrophy, reduced in hepatic disorders and as high as 700 mg. per cent in obstructive jaundice. In patients with jaundice, high temperatures and infection the blood cholesterol content was lower than in patients with the same degree of jaundice but with no infection.

Cholesterol or its products with the aid of the other lipids provide the cells with the power of holding large quantities of water without disturbing the osmotic pressure within the cells, without altering their peculiar semifluid consistency and without dissolving. Free cholesterol is an antihemolytic agent forming a weak molecular union with saponaceous substances like digitonin and hemolytic substances as saponin, other glucosides, animal venom and bile. It thus protects the blood corpuscles of the body and neutralizes the toxic action of the hemolyzing substances and lipolytic enzymes which constantly attack and digest the red blood cells. As a constituent of the sebum and waxes of the skin cholesterol protects the epidermal structures. Anemia is produced when the rate of destruction of the red blood cells surpasses the rate of regeneration. In pernicious anemia the

---

* The terms dehydrogenation and hydrogenation apply respectively to the processes of oxidation and reduction. The accepted theory today is that in the former, dehydrogenases which are present in the cells, take up hydrogen from the saturated fatty acids and deliver it to a hydrogen acceptor and thus unsaturated fatty acids result. In hydrogenation the opposite takes place and the unsaturated fats become saturated by hydrogen.

cholesterol may be reduced 50 per cent or more, and it may be restored by liver therapy.[16f]   A rise in cholesterol occurs in conditions involving either physiologic or pathologic cell multiplication.   During pregnancy both the total cholesterol and the cholesterol esters are increased.

Among the many other lipid diseases hypercholesteremia also occurs in chronic hemorrhagic nephritis, diabetes and especially in nephrosis.[16g] Barker[16h] has shown that a prolonged diet deficient in protein produces liver damage and a rise in blood cholesterol.   Cholesterol, besides its importance as an essential constituent of cells, is of great interest because of its close chemical relationship to the bile acids, vitamin D and the sex hormones.

Jones and Murray[16i] found that the addition of 2 per cent cholesterol increased the cleansing efficiency of the skin 1200 per cent as measured by its effect in removing dirt and keratin.   Cholesterol by its ability to absorb 80 per cent of water helps to form a valuable salve in which water soluble drugs may be dissolved and applied.

The cholesterol metabolism is dependent upon thyroid function as shown by the hypercholesterolemia in hypothyroidism and the reverse in hyperthyroidism.

The esterification of the cholesterol takes place in the intestinal mucosa and in the liver as shown by diseases of that organ as well as in obstruction of the biliary tract when there is a rise in free cholesterol and a corresponding decrease in cholesterol esters.

Bloor[16j] analyzed smooth, cardiac and skeletal muscles of various mammals, birds and cold-blooded animals for the cholesterol and phospholipid contents.   Smooth muscle was found to have the lowest phospholipid-cholesterol ratio whereas in cardiac and skeletal muscles the ratio was four times that amount.   Bloor concluded that "to some extent the cholesterol content may be related to spontaneous activity of smooth and cardiac muscle, and the phospholipids to energy expenditure."

In the tissues each one of the aforementioned lipids except lecithin and cephalin may be pathologically predominant.   The terms cholesterosis, cerebrosidosis or sphingomyelinosis are used to designate the specific lipid respectively involved whereas the name fatty degeneration is employed when neutral fat mainly is increased.   In xanthomatoses it is the cholesterols that are chiefly accumulated.[17]   The diaminophosphatide, sphingomyelin, is the lipid involved in Niemann-Pick's disease (splenohepatomegaly).   In this disease an enormous aggregation of sphingomyelin with a slight increase of fat and cholesterol may be found in the histiocytes and reticulum cells of almost all the organs, whereas the amount in the plasma and body fluids is normal.   In Gaucher's splenomegaly, possibly as a result of an imbalance or enzymatic disturbance,[18] there is an increased formation or decreased disintegration of the normally existing cerebroside, kerasin, whereas the sphingomyelin content is normal.   A large accumulation of kerasin occurs especially in the liver, spleen, bone marrow and lymph nodes.[19]

CLINICAL FEATURES

Xanthoma diabeticorum occurs as a rule in patients who are middle-aged, overweight and have glycosuria or a high sugar tolerance curve. The lesions, unless they are fibrotic, appear suddenly and regress fairly rapidly without leaving any trace as a result of treatment directed toward the reduction of the hyperlipemia. They occur preponderantly on the elbows, knees, buttocks and in the neighborhood of hair follicles and sebaceous glands. They are also found on other parts of the integument and buccal mucous membrane. The lesions are usually numerous, discrete, confluent or grouped and consist of pinhead to pea-sized, firm, conical or acuminate papules which have a reddish halo indicative of the inflammatory process in diabetes and which are the first to disappear with the improvement in the diabetic state. In the papulo-pustular type of this disease (extracellular cholesterosis of Urbach) the papules or nodules have yellowish solid tops resembling pustules which are frequently covered with fine telangiectatic capillaries.

The subjective symptoms vary from slight itching to tingling sensations or tenderness. Jaundice is never found and the heart is not involved. The serum is milky because of the presence of large amounts of neutral fat.

Histologic Findings. It has been emphasized by Ormsby,[20] Thannhauser[21] and others that in xanthoma diabeticorum very few or only occasional foam cells are found and the inflammatory process is more marked, whereas in xanthoma tuberosum and xanthoma disseminatum many foam cells are seen. Histologic sections of the lesions in the case (Wise and Garb[22]) of a colored woman showed on the contrary numerous xanthoma cells. Satenstein[23] stated that a differentiation could not be made histologically between the three aforementioned xanthomatous lesions.

DIFFERENTIAL DIAGNOSIS

Xanthoma diabeticorum must be differentiated mainly from xanthoma disseminatum and xanthoma tuberosum. The chief differential points aside from the distinctions in their clinical manifestations are as follows: Xanthoma diabeticorum is not a disease entity but the symptom and the result of hyperlipemia secondary to diabetes. It belongs to the group of eruptive or secondary xanthomas in contradistinction to xanthoma tuberosum and xanthoma disseminatum which are disease entities belonging to the group of primary or essential xanthomatoses and are thought to be due to a disturbance of the intracellular cholesterol metabolism.

Xanthoma tuberosum (multiplex) is an idiopathic or essential xanthomatosis of the hypercholesteremic group. The lesions appear insidiously and do not as a rule regress. The growths are nodular, from pinhead to 4 to 7 cm. in diameter, orange or carrot-yellow in color, isolated or in small groups. The surface of the lesions is usually hyperkeratotic. They are commonly found on the extensor surfaces of the elbows, hips and knees and may be of such a size as to impede the movement of these joints. They are

never seen in the axillae or bend of the elbows and knees, which are the areas of predilection of xanthoma disseminatum. They do not occur on the mucous membranes or in the larynx [24] unless they are complicated by a secondary hyperlipemia. There is no glycosuria but jaundice is frequent because of xanthomatous involvement of the liver or biliary passages. Angina pectoris and coronary sclerosis are likewise frequent complications. The serum is not milky because only the cholesterol and cholesterol esters are elevated while the neutral fat is but slightly increased. A cholesterol-free diet may help the general condition but usually has very little effect on the lesions themselves, although Montgomery [25] reported several cases which had undergone involution when a diet low in animal fat was given.

Xanthelasma of the eyelids may occur alone or together with xanthoma tuberosum with or without a lipid disturbance of other organs. A cholesterol content of the blood of over 300 mg. per cent would indicate a systemic lipid disturbance. [25a]

Xanthoma disseminatum differs from both xanthoma diabeticorum and xanthoma tuberosum. Like the latter it is also an essential xanthomatosis but of the normocholesteremic group. The lipids including cholesterol are usually within normal limits and the serum, therefore, is not milky. The lesions are widely disseminated and are situated predominantly on the flexor surfaces, on the sides of the neck, within the axillae and flexures of the knees and elbows, but not on the extensor surfaces. They are slightly raised, smooth patches consisting of about pinhead-sized papules arranged in ridges or lines so closely grouped in such areas as the neck or abdomen as to appear confluent, but on stretching of the skin are found to be separated by furrows. The color varies from maroon or chamois in the newer lesions to dark brown in the older ones. In contrast to the eruptive forms the patient is not annoyed because there is no itching or tenderness. These growths frequently involve the mucous membranes of the mouth, pharynx and larynx and may affect any organ of the body. Thannhauser and Magendantz [26] believe that lipoid proteinosis which Urbach and Wiethe described as "lipoidosis cutis et mucosae" [27] is not an independent clinical manifestation but scar tissue formation as a sequel of xanthoma disseminatum. The posterior pituitary gland, hypothalamic region or the area around the third ventricle may be invaded, interfering with the hypophyseal-hypothalamic mechanism and causing diabetes insipidus. Xanthoma disseminatum may simultaneously involve and produce defects in the membranous bones of the skull and cause exophthalmos by granulomatous masses extending forward within the orbit. Thus the triad, diabetes insipidus, exophthalmos and bone defects known as the Hand-Schüller-Christian syndrome may result though each one of the syndrome may occur alone with or without any cutaneous manifestations of disseminated xanthomatosis.

The blood vessels, heart and coronaries are not affected in this lipid disturbance. A diet low in animal fat and cholesterol has no effect on these xanthomatous lesions because the disturbance is considered to be due to a

dysfunction of cholesterol metabolism within the cell, for which no therapy is as yet known. Thyroid medication is not indicated because the blood cholesterol is normal.

CLASSIFICATION AND COMMENT ON NOMENCLATURE

Xanthoma diabeticorum was first described in 1851 by Addison and Gull.[28] Their description of the lesions is so vivid that it is worth quoting: "The eruption somewhat suddenly appeared on the arms. In the course of ten days it had extended over the arms, legs and trunk, both anteriorly and posteriorly, also over the face and into the hair. It consisted of scattered tubercles of various sizes, some being as large as a small pea, together with shining colorless papules. They were most numerous on the outside and the back of the forearm, and especially about the elbows and knees, where they were confluent. Along the inner side of the arms and thighs they were more sparingly present, and entirely absent from the flexures of the larger joints. Besides the compound character produced by the confluence of two or three tubercles, which appeared to be such, as shown by the prominent whitish nodules upon them, some looked as if they were beginning to suppurate and many were not unlike the ordinary molluscum, but when incised with a lancet they were found to consist of firm tissue which on pressure gave out no fluid save blood.

"They were of a yellowish color, mottled with a deepish rose tint and with small capillary veins here and there ramifying over them. They were accompanied with a moderate degree of irritation, hence the apices of many were rubbed and inflamed."

Malcolm Morris[29] in 1883, describing the fourth case, was first to separate the disease as distinct from but related to ordinary xanthoma. Combes and Behrman[30] suggested the name of xanthoma eruptivum because "a study of pathogenesis of the disease makes apparent the inaccuracy of the name xanthoma diabeticorum." I am of the opinion that the name xanthoma eruptivum would be confusing unless it is modified by the type of the lipid disease in question. Thannhauser[31] applies the name of eruptive xanthoma not only to the secondary xanthomas occurring as a result of hyperlipemia but also to the xanthomas occurring in some cases of xanthomatous biliary cirrhosis which belong to the primary essential xanthomatoses of the hypercholesteremic group. He differentiates secondary xanthomas following diabetic hyperlipemia from the rare cases of secondary xanthomas due to hyperlipemia in chronic pancreatitis with or without concomitant hyperglycemia and glycosuria, depending upon whether the cirrhotic changes of the pancreatic tissue also encroach upon and involve the islets of Langerhans. Both these types show a milky serum due to a great increase of neutral fat but differ in their response to insulin. In diabetic hyperlipemia insulin has a specific influence on the diabetes, hyperlipemia and the secondary xanthomas. It will clear up the diabetic state and cause a

resolution of the xanthomatous lesions. In pancreatic hyperlipemia, on the other hand, insulin will have no effect on the hyperlipemia and the secondary xanthomas may persist. It is for this type that the antilipemic hormone, lipocaic of Dragstedt and coworkers, should be tried although the results thus far have not been satisfactory. Histologically in both of these types of secondary xanthomas foam cells are found but usually not in as great numbers (case of Wise and Garb [32] excepted) as in the essential xanthomatoses. The inflammatory reaction is more prominent in the hyperlipemic type. These secondary xanthomas may also occur as a complication of the essential lipidoses and are also a part of the syndromes of Bürger and Grütz (idiopathic, familial hyperlipemia with hepatosplenomegaly and secondary xanthoma), Von Gierke's disease (glycogen storage disease) and hyperlipemia in lipoid nephrosis. The characteristics of the secondary xanthomas whether they occur as a clinical entity in xanthoma diabeticorum, with pancreatic hyperlipemia, in the aforementioned syndromes or as a complication of the essential lipidoses are all alike. That is, they are papular or nodular in type and will or will not respond to insulin and diet depending upon whether the hyperlipemia is due to a disturbance in carbohydrate metabolism or derangement of an internal fat hormone in chronic pancreatitis. When the secondary xanthomas (diabetic) occur as a complication of an essential xanthomatosis the insulin, low fat and low cholesterol diet will cause a regression in the secondary xanthomatous lesions but will have little or no effect on the original lesions of the primary xanthomatosis.

The eruptive variety occurring in some cases of xanthomatous biliary cirrhosis is papulo-pustular in type as a result of extreme hypercholesteremia with very little or no increase in neutral fat. Thannhauser [33] classifies this type as the "second type of eruptive secondary xanthoma occurring in diabetes." He calls it "extracellular cholesterosis." It conforms with the clinical appearance of eruptive xanthoma first described as xanthoma diabeticorum by Addison and Gull in 1851, the description of which has been quoted here verbatim. Although these eruptions may occur in patients with diabetes they are apparently independent of the diabetic condition because the two patients, H. L. and F. L., [34] with xanthomatous biliary cirrhosis and papulo-pustular type of xanthoma which Thannhauser describes, had normal blood sugars and no glycosuria. Histologically no foam cells are found in this type of eruptive xanthoma but lipid granules which stain orange-red with the Sudan III stain are present. Symptomatically this papulo-pustular type is characterized by severe itching in contrast to the secondary xanthomas following hyperlipemia, which usually are only slightly pruritic but are frequently tender to touch.

This discussion clearly shows that the name xanthoma eruptivum alone is not adequate as it is a general name which includes the papulo-pustular type of xanthomas complicating the primary lipidosis of xanthomatous biliary cirrhosis and the secondary xanthomas due to hyperlipemia, the latter being subdivided into diabetic hyperlipemia and the rarer hyperlipemia occur-

ring with chronic pancreatitis. Excluding those secondary xanthomas that occur as part of the syndromes previously mentioned, only the secondary xanthomas occurring with hyperlipemia due to diabetes or with chronic pancreatitis would have to be qualified thus: Xanthoma eruptivum (diabetic) and xanthoma eruptivum (pancreatic). A reasonable alternative would be to adopt the latter name only and retain the classic name of xanthoma diabeticorum for the secondary xanthomas with diabetic hyperlipemia. The eruptive xanthomas occurring in patients with xanthomatous·biliary cirrhosis would be called xanthoma eruptivum (papulo-pustular) or extracellular cholesterosis, whether they occur with diabetes or not, although Thannhauser uses the name extracellular cholesterosis for those cases of papulo-pustular type of eruptive xanthoma occurring in diabetics only.

SUMMARY

The most essential facts of lipid metabolism have been brought out to facilitate the understanding of the lipidoses and the commentary on the nomenclature of the eruptive xanthomas. Clinical differentiations among xanthoma diabeticorum, xanthoma tuberosum (multiplex) and xanthoma disseminatum have been fully described.

The name xanthoma eruptivum would not be advisable to adopt as it would include several lipid diseases with different clinical characteristics and might tend to cause confusion. The nomenclature of xanthoma eruptivum (diabetic) and xanthoma eruptivum (pancreatic) is herein recommended to differentiate between the xanthomas occurring with diabetic hyperlipemia and the xanthomas resulting from the hyperlipemia with chronic pancreatitis due to disturbance of the internal fat hormone (lipocaic). For convenience it may be advisable to adopt the latter name only and retain the classic name of xanthoma diabeticorum because of the distinctive clinical features of that metabolic disturbance.

The name extracellular cholesterosis or xanthoma eruptivum (papulo-pustular) should be applied to those eruptive xanthomas, diabetic or not, occurring with xanthomatous biliary cirrhosis which are inflammatory, very pruritic and resemble pustules but when incised are found to consist of solid tissue.

BIBLIOGRAPHY

1. PFLÜGER, cited by BODANSKY, M.: Introduction to physiological chemistry, ed. 4, 1938, John Wiley & Sons, Inc., New York, p. 200.
2. BEST, C. H., and TAYLOR, B. N.: The physiological basis of medical practice, ed. 2, 1939, Williams and Wilkins, Baltimore, p. 964.
3. VERZAR: ibid., p. 965.
4. BLOOR, W. R., cited by McPHEDRAN, W. F.: Practice of medicine, W. F. Prior Co. Inc., Hagerstown, Maryland, 1925, ix, 50.
5. Reference 2, page 1178. Also RAAB, cited by SHELTON, E. K.: The lipoid-influencing fraction, in TICE, F.: Practice of medicine, 1925, W. F. Prior Co., Inc., Hagerstown, Maryland, viii, 144.

6. BAILEY and BREMER, reference 2, p. 1177.

7. SCHOENHEIMER and RITTENBERG, reference 1, p. 345.

8. McPHEDRAN, W. F.: Obesity, reference 4.

9. Reference 1, p. 343.

10. THANNHAUSER, S. J.: Lipidosis: Diseases of the cellular metabolism, 1940, Oxford University Press, New York, p. 28.

11. Classification as used by THANNHAUSER, S. J.: ibid., p. 43.

12. Reference 10, p. 29.

13. MONTGOMERY, H., cited by SUTTON, R. L., and SUTTON, R. L., JR.: Diseases of the skin, ed. 10, 1939, C. V. Mosby Co., St. Louis, p. 389.

14. Reference 2, p. 961.

15. HOWELL, W. H., reference 2, p. 145.

16. MATTICE, M. R.: Chemical procedures for clinical laboratories, 1936, Lea and Febiger, Philadelphia, p. 89.

16a. BLOOR, W. R., and KNUDSON, A. J., cited by GRADWOHL, R. B. H.: Interpretation of cholesterol findings in blood, 1935, C. V. Mosby Co., St. Louis, pp. 167–169.

16b. Reference 10, pp. 100 and 105.

16c. ROTHSCHILD and FELSEN, cited by GRADWOHL, R. B. H.: Interpretation of cholesterol findings in blood, 1935, C. V. Mosby Co., St. Louis, pp. 167–169.

16d. Reference 10, p. 18.

16e. Reference 2, p. 963.

16f. Reference 16, p. 93.

16g. Reference 1, p. 373.

16h. BARKER, M. H., cited by ELLIOT, C. A.: Diseases of the liver, in TICE, F.: Practice of medicine, 1940, W. F. Prior Co., Hagerstown, Maryland, vii, 75.

16i. JONES, K. K., and MURRAY, D. E.: Effects of cholesterol in petrolatum on loss of water by the skin and on cleansing, in WISE, F., and SULZBERGER, M. B.: Year book of dermatology and syphilology, 1932, Year Book Publishers, Inc., Chicago, p. 510.

16j. Reference 1, p. 373.

17. PICK, and PINKUS, Reference 10, p. 42.

18. Reference 10, p. 280.

19. Reference 10, p. 265.

20. ORMSBY, OLIVER S.: Diseases of the skin, ed. 4, 1934, Lea and Febiger, Philadelphia, p. 667.

21. Reference 10, pp. 50, 68 etc.

22. WISE, F., and GARB, J.: Xanthoma diabeticorum with unusual form of eruption, report of a case, Arch. Dermat. and Syph., 1942, xlv, 723.

23. Personal communication.

24. COMBES, F. C., and BEHRMAN, H. T.: Xanthoma eruptivum (xanthoma diabeticorum), Arch. Dermat. and Syph., 1941, xliii, 936.

25. MONTGOMERY, H.: Cutaneous xanthomatosis, ANN. INT. MED., 1939, xiii, 671.

25a. Reference 10, p. 62.

26. Reference 10, p. 257.

27. WISE, F., and REIN, C. R.: Lipoidosis cutis et mucosae, Arch. Dermat. and Syph., 1938, xxxvii, 201.

28. ADDISON, T., and GULL, W.: On a certain affection of the skin, vitiligodea—(a) plana; (b) tuberosa with remarks, Guy's Hosp. Rep., 1851, vii, 265.

29. MORRIS, M.: A case of so-called xanthoma tuberosum, Trans. Path. Soc. London, 1883, xxxiv, 278.

30. Reference 24, p. 939.

31. Reference 10, p. 104.

32. Reference 22.

33. Reference 10, p. 201.

34. Reference 10, pp. 93–103.

THE INCIDENCE OF ACUTE AND SUBACUTE BACTERIAL ENDOCARDITIS IN RHEUMATIC HEART DISEASE *

By Raymond Gelfman, M.D., *Boston, Massachusetts*

It is well known that the possibility of developing acute or subacute bacterial endocarditis constitutes a decided threat to the patient with rheumatic disease.[1, 2, 3, 4, 5, 6, 7] Fully 20 to 25 per cent of all patients whose hearts have been the site of preëxisting rheumatic activity are said to fall prey to the ravages of infectious endocarditis. Moreover, 90 per cent or more of all bacterial endocarditis is found in hearts that have been previously damaged by the rheumatic infection.[5]

Believing that it might prove profitable to inquire once again into the incidence of superimposed infectious processes in rheumatic heart disease, the necropsy records of patients with evidence of old or recent rheumatic infection of the heart were analyzed, and particular reference was made to (1) sex, (2) age at time of death, and (3) age distribution. Only cases in which the diagnosis has been confirmed at autopsy are included in this series. No special emphasis is placed on the sites of preëxisting valvular lesions, as this phase has been adequately covered elsewhere.[2, 3]

The protocols of two Boston hospitals were reviewed. The period of years covered for each hospital is indicated: (1) The Peter Bent Brigham Hospital, 1913–1940, a general adult hospital which admits extremely few patients under the age of 12 years; and (2) The Infants' and Children's Hospitals, 1917–1939, with rare admissions over the age of 12 years.

The proportion of autopsies with evidence of rheumatic heart disease to the total autopsy population, and the incidence of acute and subacute bacterial endocarditis in these cases, is shown in table 1.

Rheumatic heart disease was present in 5.5 per cent of all postmortem

TABLE I

	P.B.B.H.	Child. H.	Totals
Total number autopsies	4400	3900	8300
Rheumatic heart disease number	415	37	452
Autopsy incidence R.H.D.	9.40%	0.95%	5.40%
Bacterial endocarditis number	109	6	115
Incidence B.E. in R.H.D.	26.20%	16.20%	25.40%

Key to abbreviations:

P.B.B.H.: Peter Bent Brigham Hospital.
Child. H.: Infants' and Children's Hospitals.
R.H.D.: Rheumatic heart disease.
B.E.: Bacterial endocarditis (acute and subacute).

examinations, or one in every 18 cases (452 out of 8300). This incidence was 10 times as high at the Peter Bent Brigham Hospital (9.4 per cent) as at the Children's Hospital (0.95 per cent), as might be expected from the known high incidence of rheumatic carditis in young adults.

Acute or subacute bacterial endocarditis was present in 25 per cent of these rheumatic hearts, or one in every four cases (115 out of 452). The greater frequency of this complication in adult patients (P.B.B.H. 1:4 to Children's Hosp. 1:6) is most likely due to the increasing hazard to them of superimposed infectious processes.

TABLE II

| Age Period | Rheumatic Heart Disease | | | | Bacterial Endocarditis in R.H.D. | | | | |
| | Number of Cases | | | % of Total R.H.D. Cases | Number of Cases | | | % of Total B.E. Cases | % B.E. in Total R.H.D. Deaths |
	Male	Female	Total		Male	Female	Total		
Below 10 years	17	12	29	6.4%	2	2	4	3.5%	13.8%
10–19 years	23	29	52	11.5%	5	8	13	11.3%	25.0%
20–29 years	35	33	68	15.1%	15	13	28	24.4%	41.2%
30–39 years	26	37	63	13.9%	6	9	15	13.0%	23.8%
40–49 years	50	40	90	19.9%	19	7	26	22.6%	28.9%
50–59 years	37	35	72	15.9%	6	15	21	18.3%	29.2%
60–69 years	29	25	54	12.0%	5	0	5	4.3%	9.3%
70–79 years	11	10	21 }	5.3%	1	1	2 }	2.6%	12.5%
80–89 years	1	2	3 }		0	1 ·	1 }		
Totals	229	223	452	100.0%	59	56	115	100.0%	25.4%
Average age at death	40.6	39.8	40.2		38.2	36.9	37.6		

Table 2 represents the combined data from both hospitals investigated. It notes the distribution and incidence of rheumatic heart disease and of acute and subacute bacterial endocarditis by age at time of death, for each sex separately and for both sexes together.

The distribution of males and females was equal in both the total group of 452 cases with rheumatic heart disease and in the 115 instances of bacterial endocarditis. Most deaths with evidence of rheumatic heart disease for both sexes occurred in the fifth decade. The highest incidence of deaths due to bacterial endocarditis occurred between the third and fifth decades among males, and between the second and sixth among females.

When both sexes are considered together, it is noted that the peak decade for deaths with rheumatic heart disease was the fifth. Bacterial endocarditis was not found with equal frequency in all decades. Though it was present even in the very young, and in the very old, it was particularly low under the age of 10 years, and its highest incidence occurred between the ages of 20 and 29. The average age at death was 40 years in the rheumatic series and approximately 37 years for the cases due to bacterial endocarditis.

It is difficult to evaluate properly our data as contrasted with the results

of other investigators due to the non-uniformity and variability of certain aspects of this type of study. First, most reports are based on clinical data ·of patients, both living and dead, and are not restricted as is this one, to autopsy proved material. Second, our statistics were not limited to cases of primary rheumatic heart disease as the cause of death, but rather included all cases with evidence of rheumatic infection of the heart, whether inactive or active, old or recent. Third, both acute and subacute types of bacterial endocarditis were noted, though the majority were of the subacute form of the disease. Finally, this study was concerned with bacterial endocarditis superimposed only on a rheumatic basis and did not list any case with congenital or syphilitic lesions as the primary defects.

The results of the present study, however, are essentially in accord with the data submitted in similar reports by Davis and Weiss,[3] and Laws and Levine[6] from Boston hospitals, and by Hedley[7] from Philadelphia.

SUMMARY

The necropsy records of two Boston hospitals were reviewed for the incidence of acute and subacute bacterial endocarditis in rheumatic heart disease, and special reference was made to sex, age at time of death, and age distribution.

Five and one half per cent of all postmortem examinations revealed rheumatic heart disease and 25 per cent of these rheumatic hearts had bacterial endocarditis.

Males and females were equally affected in both the total group with rheumatic heart disease and in that with bacterial endocarditis. The average age at death was 40 years for the former group and 37 years for the latter.

The frequency of bacterial endocarditis among 578 cases of rheumatic heart disease was not the same for the different decades. It was particularly low under the age of 10 and was highest between the ages of 20 and 29.

BIBLIOGRAPHY

1. BLUMER, G.: Subacute bacterial endocarditis, Medicine, 1923, ii, 105.
2. FULTON, M. N., and LEVINE, S. A.: Subacute bacterial endocarditis, with special reference to valvular lesions and previous history, Am. Jr. Med. Sci., 1932, clxxxiii, 60.
3. DAVIS, D., and WEISS, S.: The relation of subacute and acute bacterial endocarditis to rheumatic endocarditis, New England Jr. Med., 1933, xii, 619.
4. KEEFER, C.: The pathogenesis of bacterial endocarditis, Am. Heart Jr., 1940, xix, 352.
5. CHRISTIAN, H. A.: The determinative background of subacute bacterial endocarditis, Am. Jr. Med. Sci., 1941, cci, 34.
6. LAWS, C. L., and LEVINE, S. A.: Clinical notes on rheumatic heart disease with special reference to the cause of death, Am. Jr. Med. Sci., 1933, clxxxvi, 833.
7. HEDLEY, O. F.: Rheumatic heart disease in Philadelphia hospitals, Pub. Health Rep., 1940, lv, 1707.

CONCERNING THE INFECTIVITY OF SALIVA IN HUMAN RABIES [*]

By S. Edward Sulkin, Ph.D., and Carl G. Harford, M.D.,
St. Louis, Missouri

The infectiousness of saliva in rabid animals was demonstrated experimentally by Zinke, Gruner, Salm, Berendt and others in the early part of the last century. Despite the fact, however, that excessive salivation is a common feature of paralytic rabies in man, only few reports are available in the literature concerning the experimental demonstration of virus in the saliva in human rabies. Pasteur, Chamberland and Roux [1] and Raynaud and Lannelongue [2] were perhaps the first investigators to demonstrate virus in the saliva of infected human beings. More recently Palawandow and Serebrennaja [3] demonstrated the presence of the virus in the saliva of one patient with rabies by intramuscular injection into guinea pigs. At a later date [4] these investigators obtained similar results with the saliva from five additional cases of human rabies. Pawan [5] tested the saliva of six persons with symptoms of paralytic rabies. Swabs moistened with saliva were rubbed into the scarified abdominal wall of seven rabbits, all of which became paralyzed and Negri bodies were demonstrated in the respective brains. By a similar method, virus was demonstrated in the saliva of infected bovines, horses and vampire bats. On the other hand the virus may be absent in some cases, as shown recently by Sabin and Ruchman [6] who failed to demonstrate virus in the saliva of a 55 year old man who died of rabies.

The virus in human beings has been also isolated from parotid, sublingual and submaxillary glands by Pasteur, Chamberland and Roux,[7] Bardach,[8] Pace,[9] and more recently by Leach and Johnson.[10, 11]

Though Kraus, Gerlach and Schweinburg [12] and Koch [13] have pointed out that no cases of rabies have been known to result from the bite of a rabid human being, Koch refers to two cases on record of the direct transmission of the disease from one human being to another; in one instance infection took place during coitus and in the other rabies developed after a bite.

This study began on December 24, 1941, when a seven year old girl was bitten on the right leg by a stray dog. After immediate local treatment of the superficial puncture wound, Pasteur treatment was instituted. Two days later (December 26, 1941), 12 additional persons were attacked by the same dog. A laboratory examination of the brain of this animal, which was shot by the police, revealed numerous Negri bodies in the Cornu ammonis. Eleven of the 13 persons bitten by this rabid dog all received local treatment at the City Hospital followed by the Pasteur treatment, but the remaining two

could not be located.   Of the 13 individuals exposed, three died; two of these had received Pasteur treatment and one refused such treatment.   Epidemiological data are presented in table 1 and a summary of the case histories of the three persons who died follows:

TABLE I

Epidemiological Information Concerning Persons Bitten by Rabid Dog

Name	Age Sex Color	Location of Bite*†	Character of Wound	Pasteur Treatment No. of Injections	Deaths Incubation Period (days)
L. Ja.	25FW	Face Eyelid	Superficial puncture, lacerated, multiple	15	
E. De.	18MW	Right Hand	Puncture	10	
J. Yo.	30MC	Head	Deep, lacerated, multiple	12	
J. Al.	7FW	Right Leg	Superficial puncture	11	
G. Ca.	16MW	Right Arm	Puncture through clothing	10	
E. To.	46MW	Right Hand	Deep, lacerated, multiple	10	
C. Su.	66MC	Head	Superficial, lacerated	10	
E. Br.	23MW	Left Arm	Superficial puncture through clothing	10	
L. Wa.	28MC	Head Eyelid	Superficial, lacerated	15	
H. Co.	7MC	Head	Deep, lacerated, multiple	12	17
C. Va.	33MC	Head, face, lip	Deep, lacerated, multiple	11	22
J. Ha.	24MC	Lips	Deep, lacerated	None	40
L. Wa.	40FC	Right Index Finger	Deep, puncture	None	

* All persons except J. Al. exposed on December 26, 1941; J. Al. exposed on December 24, 1941.

† All persons received local treatment shortly after exposure; wounds were cauterized with phenol.

Case H. Co., a colored boy, seven years of age, was admitted to the St. Louis Children's Hospital on January 14, 1942.   Deep, lacerated multiple lesions were inflicted about the head by a stray rabid dog on December 26, 1941.   The child received local treatment at the Homer G. Phillips Hospital and Pasteur treatment was instituted shortly after exposure.   The child was given a complete course of 12 injections of the Harris vaccine.   The first symptoms of rabies were noted on January 12, 1942, the seventeenth day after exposure.   On the second day of illness, the child complained

of generalized weakness and was confined to bed. The following day the child was hospitalized and the principal symptoms were hyperirritability, apprehension, nervous jerking, visual and auditory disturbances, salivation and difficulty in swallowing. Avertin anesthesia was given soon after the patient was admitted to the hospital. The patient died 24 hours after hospitalization and no autopsy was performed.

Case C. Va., a colored man, 33 years of age, was bitten about the head on December 26, 1941, by the same stray rabid dog. Deep, lacerated, multiple lesions were inflicted on the face and lips. This person was given local treatment at the Homer G. Phillips Hospital and Pasteur treatment was started shortly after exposure. Eleven injections of Harris antirabic vaccine were given and the patient failed to return to the Clinic for the final injection to complete the course of treatment. This person first complained of left-sided weakness and difficulty in swallowing and was admitted to the hospital on January 17, 1942, 22 days after exposure. Among the prominent symptoms were vomiting, delirium, convulsions and salivation. The patient was mentally clear between convulsive seizures. The patient died within 24 hours after hospitalization. Spinal fluid was obtained for study and a specimen of ropy saliva was procured during one of the generalized convulsive seizures. No blood specimen was obtained. The patient died on the twenty-third day after exposure and a complete autopsy was performed. Numerous Negri bodies were seen in smear impressions of the Cornu ammonis.

Case J. Ha., a 24 year old colored man, was attacked by the same rabid dog on December 26, 1941. Deep lacerated wounds were inflicted on the lips. The patient received prompt local treatment at the St. Louis City Hospital, but refused to report to the Health Division for Pasteur treatment. Symptoms first appeared on February 5, 1942, forty days after exposure. The principal symptoms were hyperactivity, salivation, convulsions, photophobia and inability to swallow. Between episodes of hyperactivity, the patient would lie quietly and appear perfectly rational. During a convulsive seizure there was increased salivation and the patient had a wide-eyed stare. There was no paralysis of the extremities. The patient died 48 hours after hospitalization and a complete autopsy was performed soon after death. Numerous Negri bodies were demonstrated in the Cornu ammonis. Brain, olfactory bulbs, and salivary glands were obtained for study. Spinal fluid, blood, feces and saliva were obtained about 10 hours before death. The specimen of saliva was obtained while the patient was under heavy sedation by swabbing out the mouth and throat with absorbent cotton. Unfortunately, no specimen of saliva was obtained during a convulsive seizure.

Since several viruses (poliomyelitis,[14, 15] rabies,[16] measles,[17] influenza [18]) have been found to withstand treatment with anesthesia ether, this bactericidal agent was used to eliminate bacteria from the heavily contaminated saliva prior to intracerebral inoculation into mice. All specimens from case C. Va. were transported to the laboratory and immediately frozen and stored in the dry ice storage cabinet until ready for animal inoculation. The specimen of ropy saliva was triturated without an abrasive and using a minimum of broth. The specimen was centrifuged at 2000 r.p.m. for five minutes and the supernate was then divided into two aliquot portions. One portion was inoculated intracerebrally into six lightly anesthetized Swiss mice. Each mouse received 0.03 c.c. The second portion was treated with 10 per cent ether, shaken thoroughly, and allowed to stand in the refrigerator for two hours. After centrifugation at slow speed, the supernatant liquid below the ether layer was removed for animal inoculation. A portion of the Cornu ammonis was similarly treated and served as control of the efficiency of

the method. Undiluted spinal fluid was also injected intracerebrally into each of six Swiss mice.

The results of these animal inoculations are presented in table 2. It will be seen that 12 days after inoculation of the specimen of saliva into the mice they developed rabies-encephalitis which was identified both by symptomatology and by microscopic examination of the mouse brain.

. Examination of the brain of the patient revealed numerous Negri bodies in the Cornu ammonis and presence of virus was demonstrated by animal inoculation. After an incubation period of 11 days in mice the virus was demonstrated also in the ether treated human brain. No virus could be detected in the spinal fluid. All mice were observed for 35 days.

TABLE II

Demonstration of Rabies Virus in Tissues from Two Human Cases

Material Tested	Case C. Va.	Case J. Ha.
Saliva	2T, 2T, 3T, 12+, 14+, 18+	1T, 3T, S, S, S, S
Ether-treated Saliva	2T, 12D, 14+, 15+, 15D, S	2T, S, S, S, S, S,
Cornu ammonis	1T, 8−, 10+, 11+, 14+, 16+	11+, 11+, 12+, 13+, 14+, 14+
Ether-treated Cornu ammonis	11+, 14+, 14+, 14+, 15+, 17+	NT
Spinal fluid	S, S, S, S, S, S	S, S, S, S, S, S
Olfactory bulbs	NT	10+, 11+, 11+, 13+, 14+, 14+
Salivary gland	NT	1T, 12+, 13+, 14+, S, S
Ether-treated Feces	NT	2T, 3T, S, S, S, S

Each figure represents one mouse and the day of death.
  D = Mouse found devoured; no examination for Negri bodies made.
  T = Mouse died from trauma or of unknown complications other than rabies.
  S = Mouse survived. No Negri bodies found in brain examined after 35 days.
  + = Negri bodies found on microscopic examination.
  − = No Negri bodies found on microscopic examination.
NT = Not tested.

The specimens of saliva, spinal fluid, feces, brain, olfactory bulb and salivary gland from case J. Ha. were transported to the laboratory in a portable dry ice storage cabinet. A small amount of broth was added to the saturated absorbent cotton to facilitate expressing the saliva. The saliva was then treated with ether. The specimen of feces was similarly treated prior to animal inoculation. Cornu ammonis, olfactory bulbs and salivary glands were inoculated into mice without previous treatment with ether. From the results summarized in table 2 it will be seen that although virus was present in the brain, olfactory bulbs and salivary gland, none could be detected in the saliva, spinal fluid or feces.

The brain from each of two mice moribund on the fourteenth day after inoculation with untreated and ether-treated saliva from case C. Va. was pooled and passed to additional mice after sections were removed for microscopic examination. The brains from two mice which died on the tenth day after inoculation were pooled and titrated in mice for virus content. (0.03 c.c. of the 10^{-4} dilution killed 50 per cent of the mice after intracerebral inoculation.)

Having established the virulence of the virus recovered from the saliva and passed through two generations in mice, neutralization tests were made using (1) blood serum from case J. Ha., who received no Pasteur treatment; (2) blood serum obtained from an individual (J. Yo.) 20 days after having been bitten and 11 days after the completion of a full course of Pasteur treatment with Harris vaccine; (3) pooled serum from two rabbits hyperimmunized with the strain of rabies fixed virus * used in the preparation of the Harris vaccine; and (4) normal human serum (control). Brains from each of three mice of the third generation were removed aseptically, weighed and ground without abrasive and with sufficient beef infusion broth con-

TABLE III

Results of Neutralization Tests*

Serum Tested	Day of Death from Rabies Encephalitis†															Per Cent Survivors	Chi Square Value‡	Neutralization
J. Ha.	1T	10	11D	11	11	12	12	12	13+	14D	14	14	15	16	S	7.1	1.12	—
J. Yo.	13D	14	14	S	S	S	S	S	S	S	S	S	S	S	S	80.0	19.1	+
Hyper-immune Rabbit Serum	14	15+	S	S	S	S	S	S	S	S	S	S	S	S	S	86.6	21.99	+
Normal Human Serum	2T	9D	9	10	10	10	11+	11+	12	13	13	15	15	15	17	0		

* Undiluted serum was mixed with approximately 100 M.L.D. of virus.
† Following definite signs of involvement of nervous system.
‡ Statistical significance was determined by the calculation of the value of chi square from a four-fold table.[19]
D = Mouse found devoured.
T = Mouse died from trauma or of unknown complications other than rabies.
S = Mouse survived observation period of 35 days.
+ = Animal died from rabies proved by demonstrating Negri bodies; no symptoms observed preceding death.
Serum from J. Ha. was obtained 39 days after exposure; no Pasteur treatment; patient died of rabies.
Serum from J. Yo was obtained 20 days after exposure and 11 days after completion of Pasteur treatment.

taining 20 per cent normal horse serum to make a 20 per cent suspension by weight. After centrifugation of the pooled brain suspension for five minutes at 2000 r.p.m., serial decimal dilutions were made in beef infusion broth containing 20 per cent horse serum. Equal parts of serum to be tested and virus suspension were mixed to make a final dilution of 10^{-3} of virus. Immediately after each virus serum mixture was thoroughly mixed, 0.03 c.c. was injected intracerebrally into each of 15 Swiss mice. It will be seen from the results presented in table 3 that no specific immune bodies were present in the serum from the individual who died 40 days after exposure. Sabin and Ruchman [6] likewise found no neutralizing antibodies in the serum of an unvaccinated case of human rabies who died 20 days after

* Kindly supplied by Dr. Downey L. Harris.

exposure. Blood serum from the individual (J. Yo.) who completed the full course of Pasteur treatment, and the rabbit immune serum, contained specific neutralizing antibodies against the virus used in these protection tests. The normal human serum which was used as control contained no neutralizing antibodies for the virus.

DISCUSSION

Recovery of the virus of rabies from the saliva of a human patient confirms the previous reports that it may be present in these secretions.

Since clinical cases of human rabies require almost constant attendance, the question arose as to danger of transmission of the disease to those caring for such patients. If virus is present in the saliva of rabid patients, it would seem wise to take reasonable precautions to prevent saliva from coming into contact with wounds, abrasions, or mucous membranes of attendants.

It may be noted that the specimen of saliva that contained virus was one obtained during a convulsive seizure at which time salivation was very profuse. Incidentally, it was found to have coagulated in the tube after collection. The saliva giving a negative test for virus was obtained by swab from the mouth. This suggests that only the copious saliva during a convulsion may contain enough virus to be detected by present methods so that reported failures to recover virus may have depended on the character of the specimen used.

Mice inoculated with one of the specimens of untreated and ether-treated saliva developed rabies. That mice inoculated with untreated saliva directly into the brain did not die of bacterial infection was undoubtedly due to the absence of bacteria pathogenic for the mouse in these particular specimens.

In the identification of many viruses, immunologic tests are usually considered necessary. Serum neutralization tests are not often done in rabies because of the existence of characteristic inclusion bodies. However, specific serum tests seemed desirable in this case as a further means of identification, and also, as a means of showing that the infecting virus was immunologically the same as the strain used in the Harris-vaccine for prophylactic inoculations.

CONCLUSION

1. The virus of rabies may be present in the saliva of human cases, even if it is not always detectable by present laboratory methods.

2. Precautions should be taken by attendants to avoid contact with saliva of rabies infected patients.

BIBLIOGRAPHY

1. PASTEUR, L., CHAMBERLAND, P., and ROUX, E.: Sur une maladie nouvelle provoquée par la salive d'un enfant mort de la rage, Compt.-rend. Acad. d. sc., Paris, 1881, xcii, 159–165.

2. RAYNAUD, M., and LANNELONGUE, P.: Recherches expérimentales sur la transmission du virus rabique des l'homme au lapin, Bull. de l'Acad. de méd., Paris, 1881, x, 61–84.

3. PALAWANDOW, H., and SEREBRENNAJA, A. I.: Ueber die Anwesenheit des Tollwutvirus in menschlichen Speichel, Ztschr. f. Immunitätsforsch. u. exper. Therap., Ref., 1930, lxvi, 519–529.

    PALAWANDOW, H., and SEREBRENNAJA, A. I.: Zur Frage der Virulenz des Speichels von an Tollwut erkrankten Menschen, Ztschr. f. Immunitätsforsch. u. exper. Therap., Ref., 1930, lxviii, 236–242.

4. PALAWANDOW, H., and SEREBRENNAJA, A. I.: Ueber das Wutvirus in menschlichem Speichel, Ztschr. f. Immunitätsforsch. u. exper. Therap., Ref., 1931, lxxi, 350–351.

    PALAWANDOW, H., and SEREBRENNAJA, A. I.: Uber einige Eigentümlichkeiten der im Odessaer bakteriologischen Institute isolierten Strassenvira, Ztschr. f. Immunitätsforsch. u. exper. Therap., Ref., 1933, lxxi, 230–238.

5. PAWAN, J. L.: Infectivity of saliva in paralytic rabies, Ann. Trop. Med. and Parasitol., 1937, xxxi, 267–270.

6. SABIN, A. B., and RUCHMAN, I.: Spread of virus in an unvaccinated case of human rabies, Proc. Soc. Exper. Biol. and Med., 1940, xliv, 572–577.

7. PASTEUR, L., CHAMBERLAND, P., and ROUX, E.: Physiologie experimentale. Nouvelle communications sur la rage, Compt.-rend. Acad. d. sc., Paris, 1884, xcviii, 457–463.

8. BARDACH, J.: Nouvelles recherches sur la rage, Ann. Inst. Pasteur, 1888, ii, 9–17.

9. PACE, D.: Sur l'existence du virus rabique dans le siège de la morsue d'un enfant mort de rage, Ann. Inst. Pasteur, 1903, xvii, 293–297.

10. LEACH, C. N., and JOHNSON, H. N.: Human rabies with special reference to virus distribution and pathology, Abstracts of Communications, Third Internat. Congress for Microbiology, 1939, 325–326.

11. LEACH, C. N., and JOHNSON, H. N.: Human rabies, with special reference to virus distribution and titer, Am. Jr. Trop. Med., 1940, xx, 335–340.

12. KRAUS, R., GERLACH, F., and SCHWEINBURG, S.: Lyssa bei Mensch und Tier, Vienna, 1936, lxxx, 128–131.

13. KOCH, J.: Handbuch. der pathogenen Micro-Organismen, 1930, viii, 553.

14. AMOSS, H. L., and TAYLOR, E.: Neutralization of the virus of poliomyelitis by nasal washings, Jr. Exper. Med., 1917, xxv, 507–523.

15. KRAMER, S. D., SOBEL, A. E., GROSSMAN, L. H., and KOSKWITH, B.: Survival of virus of poliomyelitis in oral and nasal secretion of convalescents, Jr. Exper. Med., 1936, lxiv, 173–180.

16. SULKIN, S. E., and NAGLE, N.: Demonstration of rabies virus in grossly decomposed animal brains, Jr. Lab. and Clin. Med., 1939, xxv, 94–98.

17. RAKE, G., and SHAFFER, M. F.: Studies on measles. I. The use of the chorio-allantois of the developing chicken embryo, Jr. Immunol., 1940, xxxviii, 177–200.

18. SARRACINO, J. B., and SOULE, M. H.: Isolation of virus from feces of mice receiving intranasal inoculations of epidemic influenza virus, Proc. Soc. Exper. Biol. and Med., 1941, xlviii, 188–191.

19. MAINLAND, D.: The treatment of clinical and laboratory data. An introduction to statistical ideas and methods for medical and dental workers, 1938, Oliver and Boyd, Edinburgh and London.

PULMONARY TUBERCULOSIS OF THE INSANE [*]

By Joseph R. Blalock, M.D., and James B. Funkhouser, M.D.,
Marion, Virginia

Refinements in roentgenological technic making possible the rapid, inexpensive chest survey of large groups have stimulated considerable interest in the old problem of tuberculosis among the insane. The authors have made a primary survey in Southwestern State Hospital and have derived certain impressions from their experience in the subsequent management of the tuberculous patients so segregated. The initial survey has been followed by similar studies of all patients admitted since the original survey. It is felt that those now engaged in this work, or who plan work of a similar character, may be interested in our findings and observations.

Related Findings by Others

The attention of institutional psychiatrists was first directed to this unique problem by Harrington[1] in a report before the old Medico-Psychological Association in 1900, but only nine papers had appeared in the transactions when Klopp[2] reviewed the literature and presented his comprehensive report in 1927. Then only one-half of the hospitals reporting to Klopp were using roentgen-ray plates for diagnosis. Prior to this report important work had been done by Hamilton[3,4] in estimating the facilities needed by state hospitals in separately caring for the tuberculous insane, and it was generally accepted that 5 per cent of all the total beds in mental institutions should be set aside for the isolation of tuberculous patients.

During the past 15 years exact diagnostic work has been reported with more frequency.[5,6,7,8] A great many state hospitals are now engaged in a complete recheck of their patient population as regards pulmonary tuberculosis. Our survey in March 1939 was the first of several such conducted in Virginia[9] with the help and assistance of the Virginia State Department of Health. At the time of writing, three other Virginia state hospitals have completed roentgen-ray surveys.

Incidence and Magnitude

In 1927, on the basis of 106 returns on a questionnaire submitted to 163 state hospitals with reference to their facilities for diagnosis and treatment of pulmonary tuberculosis, Klopp[2] obtained figures reporting an incidence varying from 2.9 per cent in western states to 3.6 per cent in the central

states. Only 57 of the hospitals reporting used roentgen-ray. As far as we can determine, no effort was made to distinguish active from inactive cases at the time. In 1940 we [9] reported an incidence of 4.19 per cent active cases and 5.81 per cent inactive cases at the Southwestern State Hospital. Ours may be considered a primary survey because no previous comprehensive attempt had been made at this hospital to find and segregate active cases. Our figures are somewhat higher than those reported in surveys by others [8, 10] where some degree of isolation had already been in effect when the roentgen-ray survey was made.

Goldberg,[11] on the basis of Illinois state hospital statistics, estimated the incidence of pulmonary tuberculosis in insane patients to be nearly 10 times that of the general population. He surmised that "mental patients are frequently undernourished because they will not eat, they breathe shallowly, they do not exercise unless forced to do so, and the senile, arteriosclerotic and other organic cases are already at a low ebb of vitality. Here nature provides the tubercular bacilli with a fertile living culture medium." In addition to these factors, the work of Lewis [12] with dementia praecox indicates that this particular psychiatric group is constitutionally susceptible to invasion by tubercle bacilli. McGhie and Brink [5] found 47.83 per cent of their patients with dementia praecox to be tuberculous.

DIAGNOSIS: METHODS OF DETECTION

The extreme difficulty of case finding among the mentally ill was pointed out in our earlier report and has also been mentioned prominently by others.[13] Because this aspect of the problem is so important for those planning surveys, the following points are emphasized:

1. Subjective history is unreliable in mental patients. They do not have insight into such complaints as chills, fever, night sweats, cough and hemoptysis. Family histories are not always available.

2. Physical examination is very often unsatisfactory. Mental patients do not cough on direction in a proper manner nor repeat sounds to demonstrate vocal resonance. In a majority of cases they will not even remain quiet enough for a passive stethoscopic examination of the chest. Leonidoff [13] found 3.5 per cent of active tuberculosis was missed on routine physical examination.

3. Positive laboratory diagnosis is often unsatisfactory because mental patients cannot be made to understand the difference between sputum and saliva. Furthermore, they seldom cough. Our failure to obtain positive sputa even in some of our more advanced cases with cavitation confirms the experience of Bower and Schein,[14] who conclude after a special study of this aspect of diagnosis that "the sedimentation rate is a better index of the tuberculous activity than temperature, pulse or weight records." The use of routine blood sedimentation studies has proved valuable in our experience.

Oral temperature recordings for the purpose of diagnosis of pulmonary tuberculosis are certainly not reliable in mental cases for it is seldom that they will hold a mouth thermometer accurately and they are quite likely to bite or break it.

Routine temperature recordings with mentally ill patients are usually rectal temperatures, and this feature is frequently misunderstood or resisted by these patients in actual practice. It is certainly a far cry from struggling with a resistive patient for the sake of a routine rectal temperature to the simple oral, self-recording routine in vogue in sanatoria where patients are not psychiatric problems.

It may be seen from the foregoing that accurate diagnosis in the mentally ill becomes a roentgenological one. The advocates of fluoroscopy [8] claim their method to be less expensive, more rapid and nearly as accurate as the roentgen-ray plate, whereas the proponents of celluloid plates [5, 9, 10, 13] maintain that although plates are more expensive and time-consuming, they are less susceptible to individual examiner's skill, and, moreover, form a permanent record. Miniature 35 millimeter fluorogram seems to be admirably adapted to survey work. However, the various technics have been carefully studied by Larkey [15] and Mercer,[16] who conclude that the standard 14 by 17 inch celluloid film has not been surpassed in reliability.

Our original survey was made on paper films, a method which possesses the advantage of economy and speed at only a slight sacrifice of diagnostic validity. Questionable and debatable films were later checked with celluloid films. After the first survey, however, all of our studies have been made on 14 by 17 inch celluloid plates and we have continued since the survey to make a routine flat plate of the chest on each new hospital admission (and new employee). It is only by doing this that our survey work could be kept up to date, and it may be stated here that, aside from tuberculosis, many incidental findings in regard to the heart, aorta and bony thorax have been brought to light that were not detected on routine physical examination.

Yet even roentgenological diagnosis presents special problems when dealing with mental patients. Exact centering of the plate, proper posture and position of the subject, the correct phase of respiration, are technical details that must frequently be foregone.

MANAGEMENT AND TREATMENT

An honest attempt to approximate the treatment conditions in general usage in sanatoria was at first made. We soon learned, however, that the time-honored sheet anchor of tuberculosis, bed rest, is, with few exceptions, impossible to maintain. Sane persons may be reasoned with, coaxed or threatened into staying in bed but psychiatric patients are not usually susceptible to coaxing, may be incapable of rational fear, and are not amenable to firmness. Such refinements as sand bags and voluntary vocal silence are too often impractical in a mental institution. Restraint by force usually

defeats its own ends. A few of our patients do remain in bed, it is true, and all of our cases who have active disease are encouraged to do so, but the majority cannot be kept in bed.

Strangely enough, many of our mentally depressed patients with active tuberculosis, who do not improve on a regimen of bed rest, show a weight gain, increased appetite and general clinical improvement when they are encouraged to get out of bed.

Our experience with artificial pneumothorax has led us to believe that this procedure is of particular importance in the treatment of the tuberculous insane. Here we find ourselves in distinct disagreement with Alexander, who lists insanity as a contraindication to pneumothorax.[17] Before we began the collapse treatment, we were fearful that it would not be applicable to mentally diseased cases, but today we are beginning to realize that pneumothorax has a particular value in selected cases. For example, we have been able to maintain several of our pneumothorax cases throughout manic attacks, thus preserving diseased lungs from the dangers of hyperventilation. Many of our pneumothorax patients are too deteriorated to coöperate with the classical "rest cure" but their diseased lungs are at rest by virtue of the gas compression.

Of course all the active cases are given a higher caloric and vitamin diet than the general hospital population. They are not permitted to do any strenuous work, and occupational therapy is carefully moderated. Even when bed rest is absolutely impossible to maintain, activity is discouraged in those patients who are not showing improvement.

RESULTS

(a) *Survey of Hospital Patient Population.* On March 24 and 25, 1939, using paper films, 1095 of the 1263 patients at Southwestern State

TABLE I

Survey Data: Incidence of Tuberculosis

	Male		Female		Total	
	No.	%	No.	%	No.	%
Positive tuberculosis, all stages	34	7.7	77	13.7	131	10.4
A. Active	29	4.1	24	4.3	53	4.2
1. Minimal	9	1.3	11	2.0	20	1.6
2. Moderately advanced	13	1.9	10	1.8	23	1.8
3. Far advanced	7	1.0	3	0.5	10	0.9
B. Inactive	25	3.6	53	9.4	78	6.2
1. Minimal	22	3.1	45	8.0	67	5.3
2. Moderately advanced	2	0.3	7	1.2	9	0.7
3. Far advanced	1	0.1	1	0.2	2	0.2
Non-tuberculous lesions including healed lesions suspicious of tuberculosis, later shown not tuberculosis	210	30.0	259	46.1	469	37.1
Entirely negative	437	62.3	226	40.2	663	52.5
All patients examined	701	100.0	562	100.0	1263	100.0

Hospital were roentgen-rayed. The remainder were roentgen-rayed, and poor and debatable films were retaken during the next few weeks. In table 1 the findings of this survey are summarized. The more detailed breakdown of this study is given in table 1 and a briefer tabulation of these findings in table 2.

TABLE II

Summary of Survey Data: Incidence of Tuberculosis
In per cent

	Male	Female	Total
Positive tuberculosis, active................................	4.1	4.3	4.2
Positive tuberculosis, inactive............................	3.6	9.4	6.2
Non-tuberculous lesions....................................	30.0	46.1	37.1
Negative..	62.3	40.2	52.5
	100.0	100.0	100.0

(b) Since the completion of the above survey of those patients residing in the hospital we have routinely roentgen-rayed the chests of all newly admitted patients. This amounts to 1181 patients in the three-year period embracing March 25, 1939 to March 24, 1942. In table 3 are given the

TABLE III

Comparison of Initial Roentgen-Ray Survey with Roentgen-Ray of Admissions
for Three Consecutive Years

	Original Survey		Consecutive Admissions	
	No.	%	No.	%
All chest films..................................	1263		1156	
Entirely negative for tuberculosis*..	1132	89.6	1026	88.8
Positive tuberculosis all stages..................	131	10.4	130	11.2
a. roentgenologically active................	53	4.2	44	3.8
b. roentgenologically inactive..............	78	6.2	86	7.4

* Includes other abnormalities, and healed lesions suspicious of tuberculosis, later found not tuberculosis.

comparative findings in these two groups. It will be seen that among the serial admissions having roentgen-ray evidence of tuberculosis 3.8 per cent were roentgenologically active, as compared with 4.2 per cent in the original survey. When the inactive cases were considered the greater percentage of 7.4 occurred among the consecutive admissions as compared with the 6.2 per cent found among those residing in the hospital.

These figures would indicate not only that the incidence of pulmonary tuberculosis is high among the mentally ill who have been in the hospital for a long time but also that the incidence is approximately as high at the time these patients are first admitted to the hospital.

McGhie and Brink [5] feel that the too often necessary overcrowding in many state hospitals contributes to the high incidence of tuberculosis in mental institutions. Bogan and others [6] have suggested that most mental patients contract their illness after admission to a mental hospital. Our findings suggest that although these facts may be true the increased incidence of pulmonary tuberculosis is already a major factor at the time of admission.

(c) *Follow-up Studies.* Of the 53 cases active in March 1939, 11 were dead on September 17, 1941, two of pulmonary tuberculosis, nine of other conditions, in which pulmonary tuberculosis was considered a secondary cause of death. Sixteen of these 53 originally active cases were stationary. Six showed a definite spread and 16 were improved. One had completely cleared and three cases were discharged from the hospital before a recheck could be made, and their status was unknown.

Of the originally inactive cases · (March 1939) totalling 136, only 48 were in the hospital at the time we rechecked the chests two and a half years later, the others having died from other causes or left the hospital by furlough or discharge. Of these 48 all were roentgenologically stationary except eight. Two of these eight showed a definite reactivation and were reclassified. Three were improved, the lesions being more compact and healed and three were classified as non-tuberculous lesions.

Because the majority of our active treatment cases (pneumothorax) were still undergoing weekly gas injections, we could not state with accuracy the full and final effects of our artificial collapse therapy. The total number of cases treated by collapse amounted to 18, with no deaths and only two major complications (one massive subcutaneous emphysema and one spontaneous pneumothorax). Over 1180 refills had been given. Five of the 18 cases had been discontinued for various reasons, and of the five the lungs of four appeared to be arrested roentgenologically. One of the reëxpanded lungs showed no improvement.

In nearly every instance patients confined in the tuberculosis building, where extra diet is provided and an attempt at a "rest hour" is made, had gained weight and appeared to be clinically improved.

It must be admitted, however, that the above results would not compare favorably with a group of non-psychotic tuberculosis patients, particularly in view of the fact that nearly half of our active cases were only minimal when first detected. (Minimal 45; moderately advanced 27; far advanced 22.)

Results cannot be measured, however, purely in terms of cases cured, arrested and improved. The advantage of isolation to the non-tuberculous patients and personnel is incalculable. A glance at our figures will show that one out of every 24 routine chest plates has shown up a case of active pulmonary tuberculosis. Certainly the time and expense of making two dozen roentgenograms is justified when by so doing an active case of pulmonary tuberculosis is isolated and given adequate treatment, at the same time protecting patients on other hospital wards.

SUMMARY AND CONCLUSION

On the basis of our primary survey of a representative state hospital for mental patients, and the figures published for comparable surveys, we believe that the incidence of roentgenological active pulmonary tuberculosis among the insane is at least 4 per cent. We have evidence which tends to suggest that this high incidence bears some relation to mental disease itself and that it is not due to institutionalization. A comparison of the incidence of active pulmonary tuberculosis as shown by roentgen-ray in a cross section survey of the hospital population with a series of new admissions shows the incidence of each to be 4.2 per cent and 3.8 per cent respectively while the incidence of inactive pulmonary tuberculosis is 6.2 per cent and 7.4 per cent respectively. Because of the inability of the large majority of mental patients to coöperate with physical examination or to produce sputum for examination, we are convinced that the only positive and thoroughly accurate method of detecting pulmonary tuberculosis in all types of mental patients is by means of the roentgen-ray, either by fluoroscopy, fluorogram or by standard size celluloid plates, the latter being the method of choice.

In our experience it has not been found possible to treat institutional mental patients having pulmonary tuberculosis by the methods in general use for sane patients with the same degree of success. Furthermore, it is felt that artificial collapse has particular merit.

Tuberculosis in state hospitals is a larger problem than has been generally recognized. It is to be expected that 4 per cent of the patients will have active pulmonary tuberculosis. Unless these patients are found, they constitute a source of contagion to the entire population.

BIBLIOGRAPHY

1. HARRINGTON, ARTHUR H.: Separate provisions for tuberculous patients in state hospitals for the insane, Trans. Am. Medico-Psychol. Assoc., 1900, vii, 203.
2. KLOPP, HENRY I.: The care of tuberculous patients in mental hospitals, Am. Jr. Psychiat., 1927, vi, 641.
3. HAMILTON, S. W.: A building for tuberculosis at Hudson River State Hospital, Modern Hosp., 1923, xxi, 590.
4. HAMILTON, S. W., and KIDNER, T. B.: Buildings for the tuberculous insane, Technical Series No. 4, National Tuberculosis Association, 1925.
5. McGHIE, B. T., and BRINK, G. C.: A tuberculosis survey in mental hospitals, Am. Jr. Psychiat., 1934, xc, 975.
6. BOGAN, T., TIETZ, E. B., and GRACE, F.: Tuberculosis and mental disease, Am. Rev. Tuberc., 1934, xxx, 351.
7. BURNS, H. A.: Incidence of tuberculosis in state institutions in Minnesota, Am. Rev. Tuberc., 1936, xxxiii, 813.
8. HARRISON, D. A., and SCHEIN, G.: Report of tuberculosis survey at Marcy State Hosp., Psychiat. Quart., 1937, ix, 637.
9. BLALOCK, J. R., FUNKHOUSER, J. B., and FLANNAGAN, J. E. K.: The incidence of pulmonary tuberculosis in Southwestern State Hospital, Virginia Med. Monthly, 1940, lxvii, 465.

10. WICKS, C. A.: Tuberculosis prevention and treatment in Ontario Mental Hospitals, Am. Jr. Psychiat., 1940, xcvi, 1335.
11. GOLDBERG, BENJAMIN: Clinical tuberculosis, 1939, ii, M 15, F. A. Davis Co., Philadelphia.
12. LEWIS, NOLAN D. C.: Constitutional factors in dementia praecox, Nerv. and Ment. Dis. Monograph Series, 1923, No. 35.
13. LEONIDOFF, A. A.: Control of tuberculosis in Hudson River State Hospital, Psychiat. Quart., 1938, xii, 754.
14. BOWER, G. C., and SCHEIN, G.: The sedimentation test in psychotic patients with pulmonary tuberculosis, Psychiat. Quart., 1935, ix, 263.
15. LARKEY, S. V.: The National Research Council on Medical Preparedness, War Med., 1940, i, 77.
16. MERCER, NELSON: Choosing a method for mass x-raying of service men, Virginia Med. Monthly, 1941, lxviii, 589.
17. ALEXANDER, JOHN: The collapse therapy of pulmonary tuberculosis, 1937, C. C. Thomas, Baltimore, 224.

COMBINED ELECTROCARDIOGRAPHY, STETHOG-RAPHY AND CARDIOSCOPY IN THE EARLY DIAGNOSIS OF HEART DISEASE *

By Walter M. Bartlett, M.D., F.A.C.P.,† and J. Bailey Carter, M.D., F.A.C.P.,‡ *Atlanta, Georgia*

In the diagnosis of heart disease the mind attaches greatest importance to the phenomena that most strongly affect the senses. A roaring murmur or an irregular pulse thrusts itself upon our attention. Diagnostic signs, however, may be so slight that most careful methods are required for their detection.[1]

A synchronized heart sound tracing and electrocardiogram, as an aid in diagnosis, presents distinct advantages. It enables the examiner to better correlate clinical findings. The procedure is unique in the field of diagnosis. Portable equipment permits the physician, at the bedside, to readily substantiate or correct his clinical impressions. An objective aid, so simple and so easily applied, greatly increases the clinician's diagnostic acumen.

We have shown[2] that combined graphic methods constitute a useful adjunct to the routine examination of applicants for flight training. With the aid of these accessory methods of examination, early, otherwise unrecognized heart disease may be detected. Many organic murmurs are overlooked or ignored in routine examinations. Although approximately 25 per cent of systolic murmurs are of significance, only 10 per cent of these are recorded. Graphic records give objective proof of their existence and are of diagnostic assistance. The cardioscope permits the skilled interpreter instantly to recognize and accurately to classify arrhythmias, heart blocks and tachycardias. In 80 per cent of 10 cases of heart disease in a series of 200 pilots examined the electrocardiogram was essential for diagnosis. A stethogram was essential for diagnosis in 20 per cent of the 10 cases. Combined graphic methods were helpful in 70 per cent of these previously undiscovered cases of heart disease. No simple diagnostic aid gives more valuable assistance.

Rappaport and Sprague[3] found that tones of different frequency but of similar intensity affect the human ear differently. The human ear is a better detector of changes in frequency than of changes in intensity. They conclude that the major advantage of the amplifying stethoscope over the acoustic stethoscope is that it enables one to adjust the intensity to the de-

sired level and thus eliminate modifying characteristics which otherwise can not be overcome.

Mannheimer [4] states that calibrated stethography promises to become a valuable aid in differentiating organic and functional murmurs. We have found that organic murmurs are apt to be associated with abnormalities in heart sounds as well as in the electrocardiogram. Murmurs associated with diminution, obliteration or abnormal accentuation of heart sounds lead us to suspect organic disease. Heart sounds are seldom obliterated by a functional murmur.

Arenberg [5] reports 200 cases examined clinically and checked by graphic methods. He feels that the stethogram is no more dependable than is the ear for differentiating organic and functional murmurs. He has not observed that the stethogram can detect changes in heart sounds associated with a murmur which otherwise might escape detection. A prolonged rasping murmur, loud in the aortic area and transmitted to the neck, was described as systolic by five competent clinicians, two of whom also described a diastolic murmur in the third left interspace at the edge of the sternum. A stethogram showed a diastolic murmur. The first heart sound was found to be inaudible, the reduplicated and accentuated second sound being superimposed upon the loud diastolic murmur at its very beginning. This is but one example of the critical judgment which a stethogram may add in the timing of murmurs; a typical instance of the importance of marked heart sound distortion in the differentiation of an organic from a functional murmur. We have found it advantageous routinely to record heart sounds and murmurs in all valve areas. The microphone, as well as our ears, may detect these sounds better in one than in another area. Commonly an aortic murmur is better recorded along the left sternal border than in the classic aortic area. Similar observations concern mitral sounds and murmurs. This may explain the difficulty experienced at times in recording clinical murmurs. Although clinical and stethographic findings are closely correlated, we have found many murmurs that have escaped the ear of the examiner.

METHOD

We have examined 1108 patients with heart disease. Clinical findings were recorded at the time of examination in all instances. Cardioscopy, for rapid classification, followed by combined electrocardiography and stethography, was employed.

The technic was the same as that previously described (plate 1).[2] With the patient in the recumbent position [6, 7] the three standard (limb) leads were recorded. A simplified method,[8] modified from Roth,[9] was employed for recording chest leads.[10] The left arm electrode was removed and applied to the left chest in the fifth interspace at the midclavicular line, lead wire connections remaining undisturbed. The electrode was held in place by the

left fingers of the patient or an assistant, lightly applied to the overlying folded rubber strap. Lead I and Lead III on the control board were selected in turn, a Lead CR_4 and Lead V (inverted CF_4) being recorded in succession. We have found these companion leads most practical for routine clinical use. The stethogram of the mitral area was recorded with Lead I of the electrocardiogram; with Lead II, the microphone was placed over the pulmonic area; with Lead III, aortic sounds were recorded; tricuspid sounds were recorded simultaneously with CR_4. Both conventional (25 mm.) and fast speed (75 mm. per sec.) records were used to reveal more definitely the graphic details of the various heart sounds.

Our patients varied in age from 2 to 87 years, 1048 being adults. The 1108 cases examined have been classified according to table 1. We carefully correlated clinical and stethographic findings in each instance. Our

TABLE I

Diagnosis in 1108. Patients Studied

	Rheumatic	Syphilitic	Arterio-sclerotic*	Congenital	Undetermined
No. of Pts.................	308	117	649	14	20

* Including hypertensive heart disease and coronary artery disease.

TABLE II

Criteria for Normal Heart Sounds

First Sound:	5–11 vibrations	duration 0.06 to 0.11 sec.
Second Sound:	3–4 vibrations	duration 0.04 to 0.06 sec.
Third Sound:	1–3 vibrations—taking place 0.11 to 0.14 sec. after the beginning of the second sound.
Systolic Murmurs:	13–35 vibrations—or more, up to or through second sound if of long duration; if short 0.02 to 0.03 sec. beyond the first sound.
Diastolic Murmurs:	7–45 vibrations—when counted with the second sound—duration 0.07 sec. or throughout diastole or occupying any portion thereof.

criteria for normal heart sounds were those advocated by Orias-Menendez,[11] Wiggers,[12] Boyer, Eckstein and Wiggers,[13] and Pazzanese,[14] summarized in table 2.

In 88 per cent of the cases clinical and graphic findings agree. In 12 per cent the stethogram was essential for diagnosis. Particularly was this true of gallop rhythm and early mitral stenosis or aortic insufficiency. In 390 (35 per cent) of the cases stethograms were helpful in diagnosis, otherwise undetected abnormalities of heart sounds being recorded. In no case was a systolic or diastolic murmur heard that was not satisfactorily recorded. The fact that "the murmurs so often look just as they sound" was striking. Sketches of the sounds as heard clinically, when compared with the stethogram, usually have been in accord.

In 731 (66 per cent) of the cases, the electrocardiogram was of assistance in establishing the diagnosis. The value of chest leads increases

in direct proportion to the age of the patient. Between ages 31 and 41, 20 per cent and between 61 and 87, 47 per cent of chest leads were abnormal. Chest leads were abnormal in 29 per cent, confirmatory in 24 per cent and of diagnostic assistance in 5 per cent of the cases examined.

In 42 per cent of the 102 cases of gallop rhythm the timing of the extra sound was misjudged clinically. Stethography established 37 of these as protodiastolic, 29 as presystolic, seven as systolic, two as summation gallop, and 18 graphs showed a prominent auricular sound often with the associated graphic changes of a coronary occlusion. In nine cases a prominent physiologic third sound was mistaken clinically for a gallop sound. Stethography is the only dependable method for differentiating these extra sounds. It is essential for the accurate diagnosis of gallop rhythm.

Extraneous vibrations, i.e., pulmonary sounds, the râles of emphysema, asthmatic wheezing or whistling râles and breath sounds of the dyspneic patient are easily recognized since they are not synchronous with cardiac activity as simultaneously recorded in the electrocardiogram. The ease with which sounds of cardiac and non-cardiac origin can be distinguished is well illustrated by the case of paroxysmal diaphragmatic flutter recently reported by Goodman.[15]

Routine venous pulse tracings were found unnecessary from a clinical standpoint since the intervals established by our criteria were found to be reliable. Our aim has been to simplify rather than complicate a practical routine procedure. Our graphs were recorded under the usual conditions of the home, office, clinic, or hospital, rather than in a sound-proof studio so rarely available for routine clinical examinations. Since operation of the equipment is independent of an outside electrical source it is available for use in field hospital, aeroplane or rural district.

Screening of the general population for hidden cases of tuberculosis and syphilis has become increasingly popular during recent years. Great strides have been made in the control of these infections. With the aid of the cardioscope similar screening for heart disease can be done. A combined electrocardio-stethogram may or may not be recorded, depending upon abnormal or normal cardioscopic findings.

When instantaneous visualization is used chest leads need not be taken if the findings are normal in the cardioscope. When this equipment is not available or if a trained observer is not present to interpret cardioscopic findings, chest leads should be routinely recorded, since no one can know their value in advance. Whereas the cardioscope may be used to determine these changes, our experience has justified the routine use of the companion chest leads described.

A trained technician and interpreter can examine 120 patients during an eight hour day (plate 1). The number of "positives" would probably exceed those found in other types of public health examinations. Results of routine induction examinations of 310 national guardsmen emphasized the

value of the method in searching for obscure heart disease, particularly of the rheumatic type. In four of the five cases having electrocardio-stethograms serious heart disease was revealed. Other cases might have been detected had routine graphic methods been employed.

To attempt to determine the presence or absence of heart disease by examination in an armory or other unsuitable place is often difficult. Excitement, tachycardia, malingering, or the effects of a farewell debauch may be disturbing factors. Cardioscopy, combined graphic records or both
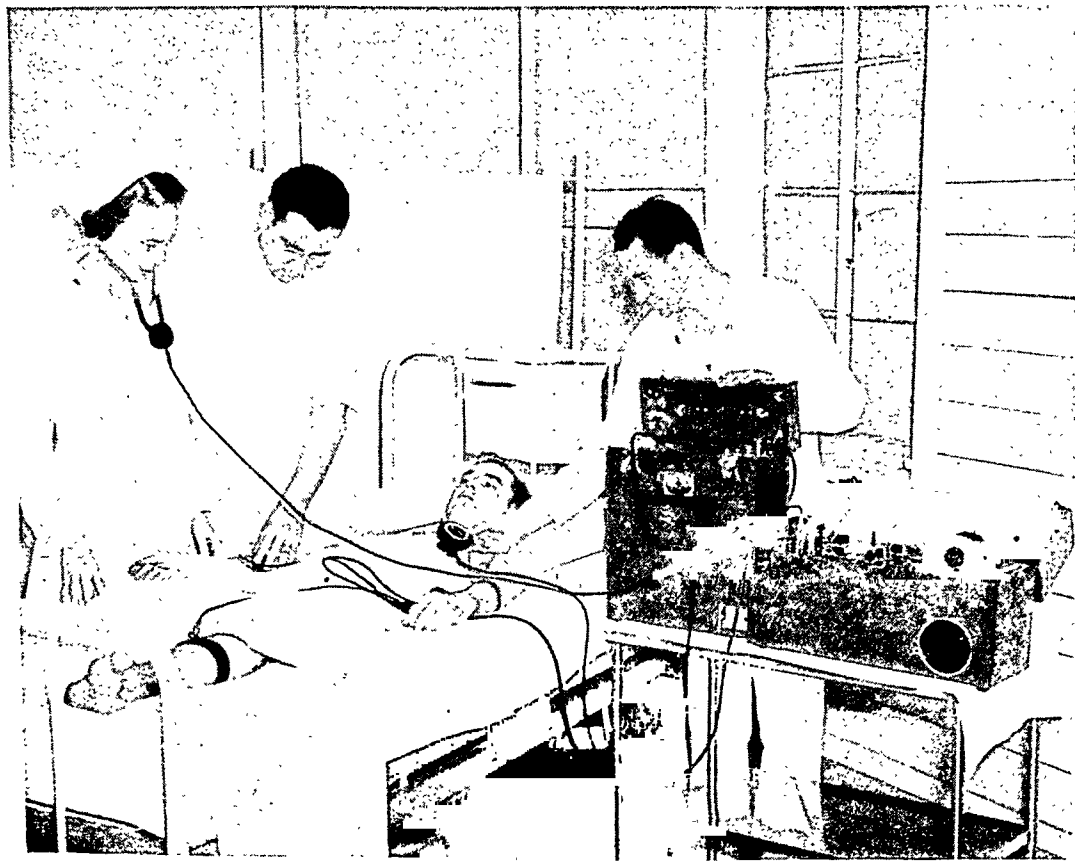
PLATE 1. View of the equipment for taking combined graphic records illustrating how the nurse or physician may listen to the heart sounds and murmurs through the amplifying stethoscope. After the intensity is adjusted properly, it is often possible to hear murmurs missed by the usual acoustic stethoscopic technic. (Photo by Signal Corps, U. S. Army.)

under these circumstances are of distinct advantage in detecting organic heart disease, either active or clinically quiescent but subject to aggravation by active military duty.

It is anticipated that in the near future visualization by means of a double beam cardioscope will give instantly a view of the electrocardio-stethogram so that with properly adjusted audiophones, more than one examiner can visualize the sound track synchronized with the electrocardiogram and listen to heart tones and murmurs at the same time.

CASE REPORTS

Case 1. White female, aged 38, on first visit to clinic, June 16, 1936, complained of palpitation with increasingly severe dyspnea of six years' duration and orthopnea of three months' duration, with marked nervousness, loss of weight and appetite. She had been confined to bed for three months at the age of 15 with rheumatic fever. Subsequent attacks of tonsillitis had occurred.

She was poorly nourished. Pulse was 85 per minute and regular. Blood pressure was 110 mm. Hg systolic and 75–70 mm. diastolic. Heart was slightly enlarged to right and left. Apex beat was forceful. A short apical presystolic murmur and a loud aortic systolic murmur were present. Tonsils were large and septic. No other significant findings. A diagnosis of rheumatic mitral disease was made.

Except for extrasystoles, electrocardiograms were repeatedly considered normal. The combined record (figure 1) shows a short faint presystolic murmur in the mitral area, a long loud systolic murmur and a short early diastolic murmur during the first third of diastole in the pulmonic and aortic areas. The aortic second sound is not prominent and is rendered inaudible by the diastolic murmur. This probably explains why a diastolic murmur was not heard.

Case 2. Colored female, aged 38, came to the clinic March 7, 1940, and complained of progressive dyspnea on exertion, inability to sleep on her left side and pain in the right shoulder and arm of three weeks' duration.

She was well developed, well nourished and slightly dyspneic. The apex beat was 2 cm. beyond the left midclavicular line in the sixth interspace. The heart was slightly enlarged to the right. A systolic murmur was heard in the mitral and aortic area, the latter being transmitted to the vessels of the neck. Despite the dyspnea and loud systolic murmur she was assured that her trouble was "rheumatism" of the right shoulder; not heart disease. Our clinical opinion, one week later, was that she had an aortic lesion with possible dilatation.

A stethogram (figure 2) revealed a loud crescendo-decrescendo systolic murmur with an accentuated second sound most marked in the aortic area. The electrocardiogram showed an intraventricular block with left axis deviation. The sound record is of particular interest because it shows a prominent auricular sound which could not be heard, a reduplicated first aortic sound which was obscured by the loud murmur and vibrations suggesting an inaudible diastolic murmur in the aortic area. Stenosis and insufficiency of the aortic valve were considered probable. An aortic aneurysm was demonstrated by fluoroscopy.

Had it not been for the dyspnea on exertion, since the systolic murmurs were ignored, the diagnosis might have been missed. The case probably would not have been recognized as heart disease. The diagnosis was established mainly by supplementary aids. We have not seen a functional systolic murmur of this configuration and associated with such changes in heart sounds.

Case 3. Colored female, aged 55, first seen on June 2, 1933, complained of hot flashes, headaches, nervousness and shortness of breath of six months' duration.

She was well nourished and not dyspneic but appeared chronically ill. The pupils were fixed to light. The heart was enlarged to the left. Apex beat was visible 3 cm. beyond the left midclavicular line in the sixth interspace. Marked pulsation of the carotids with slight suprasternal pulsation was present. The peripheral arteries were definitely sclerotic. Blood pressure was 210 mm. Hg systolic and 100 mm. diastolic. During the following seven years many clinic physicians consistently recorded a loud systolic murmur in the aortic area transmitted to the vessels of the neck. A diagnosis of aortitis, probably syphilitic, was made. On February 28, 1940, we reëxamined this patient and confirmed the previous findings of a loud systolic murmur. No diastolic murmur was heard.
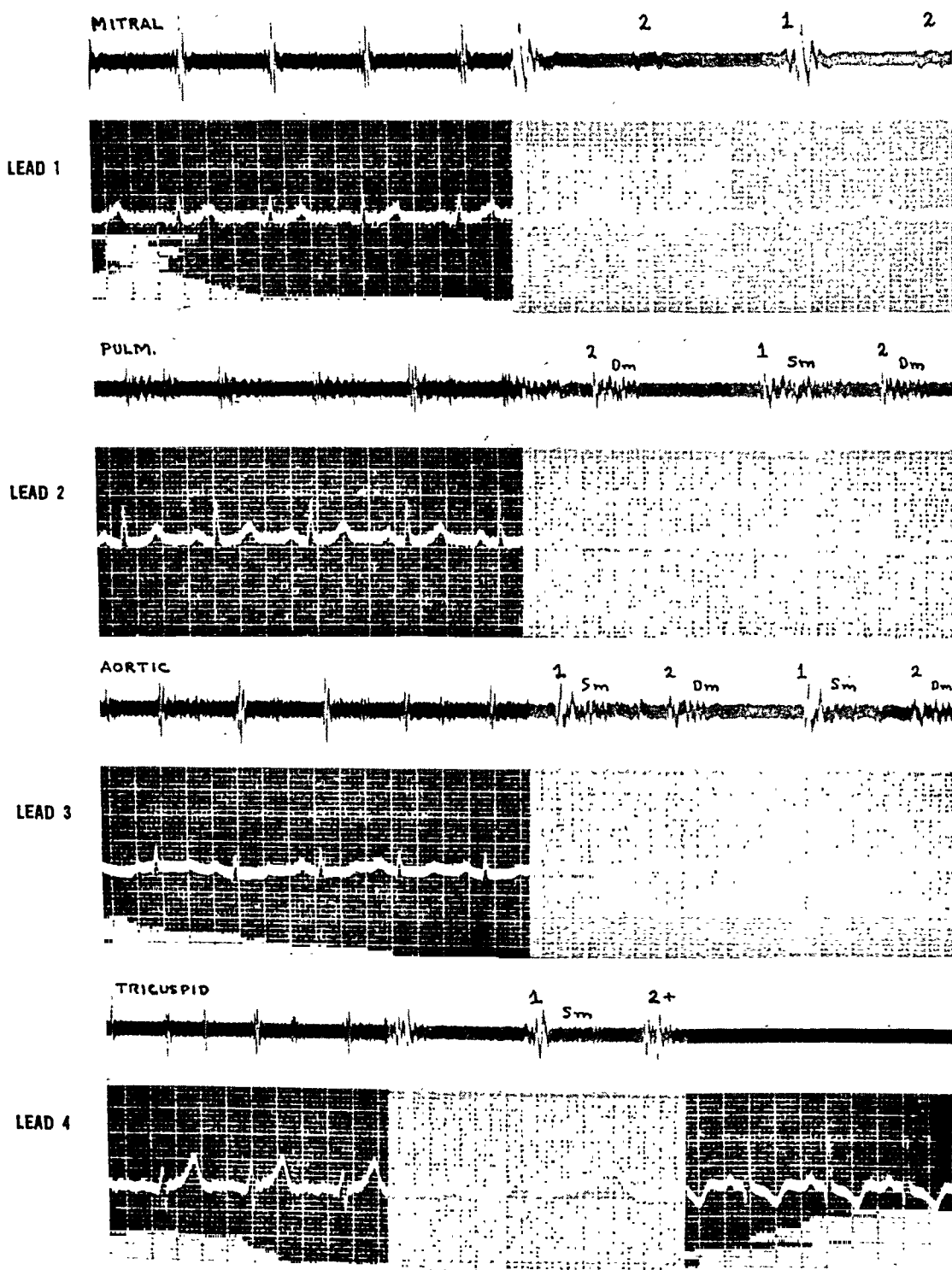
FIG. 1. Case 1.

The stethogram (figure 3) showed a hitherto unrecognized presystolic murmur in the mitral area, a systolic murmur in all areas but most prominent in the aortic area, accentuated aortic and pulmonic second sounds and vibrations suggesting an
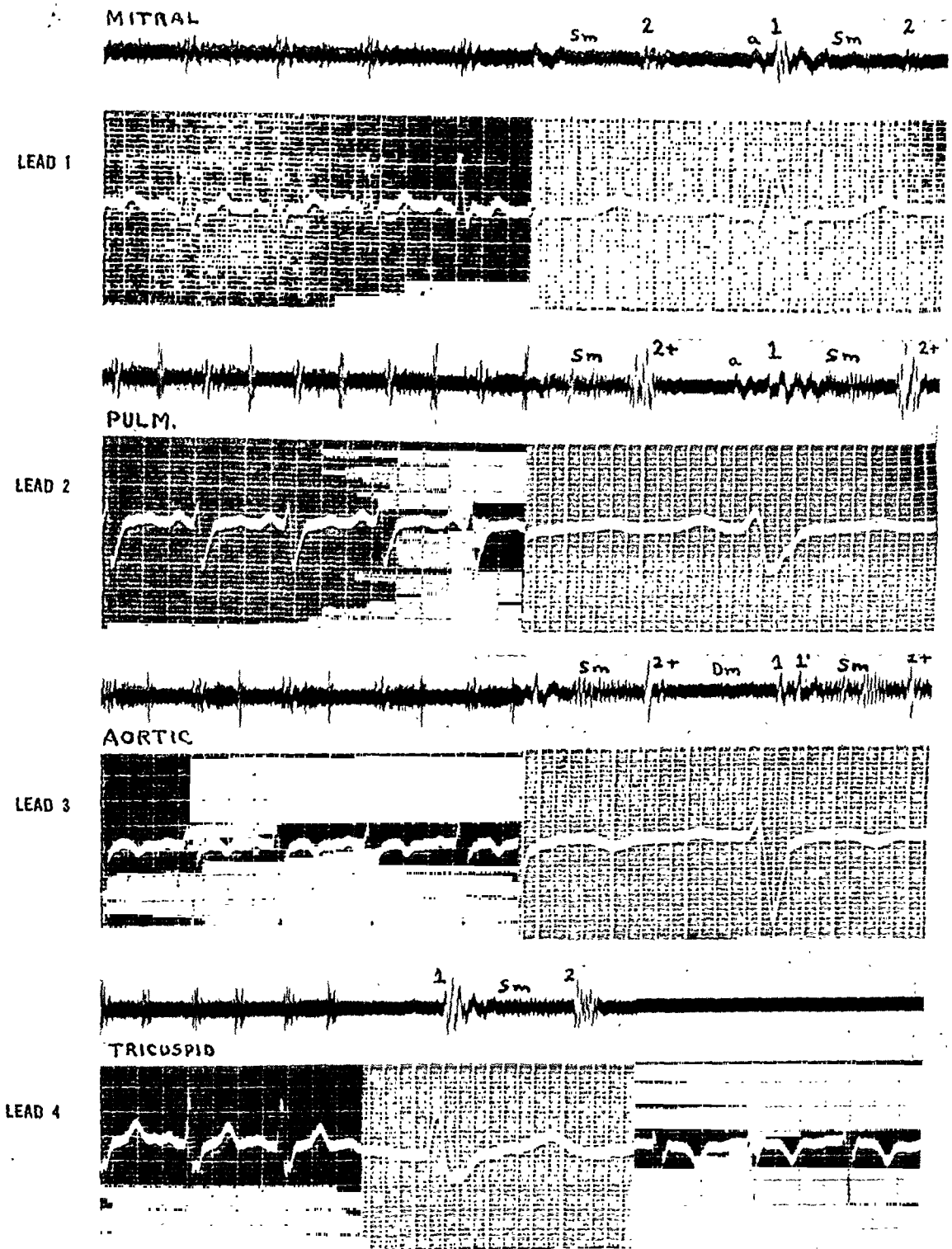
FIG. 2.   Case 2.

early diastolic murmur in the aortic area. The aortic systolic murmur was of the decrescendo type which is often described as blowing since it fades away as the second sound approaches. The presystolic mitral murmur, definite in the sound tracing,
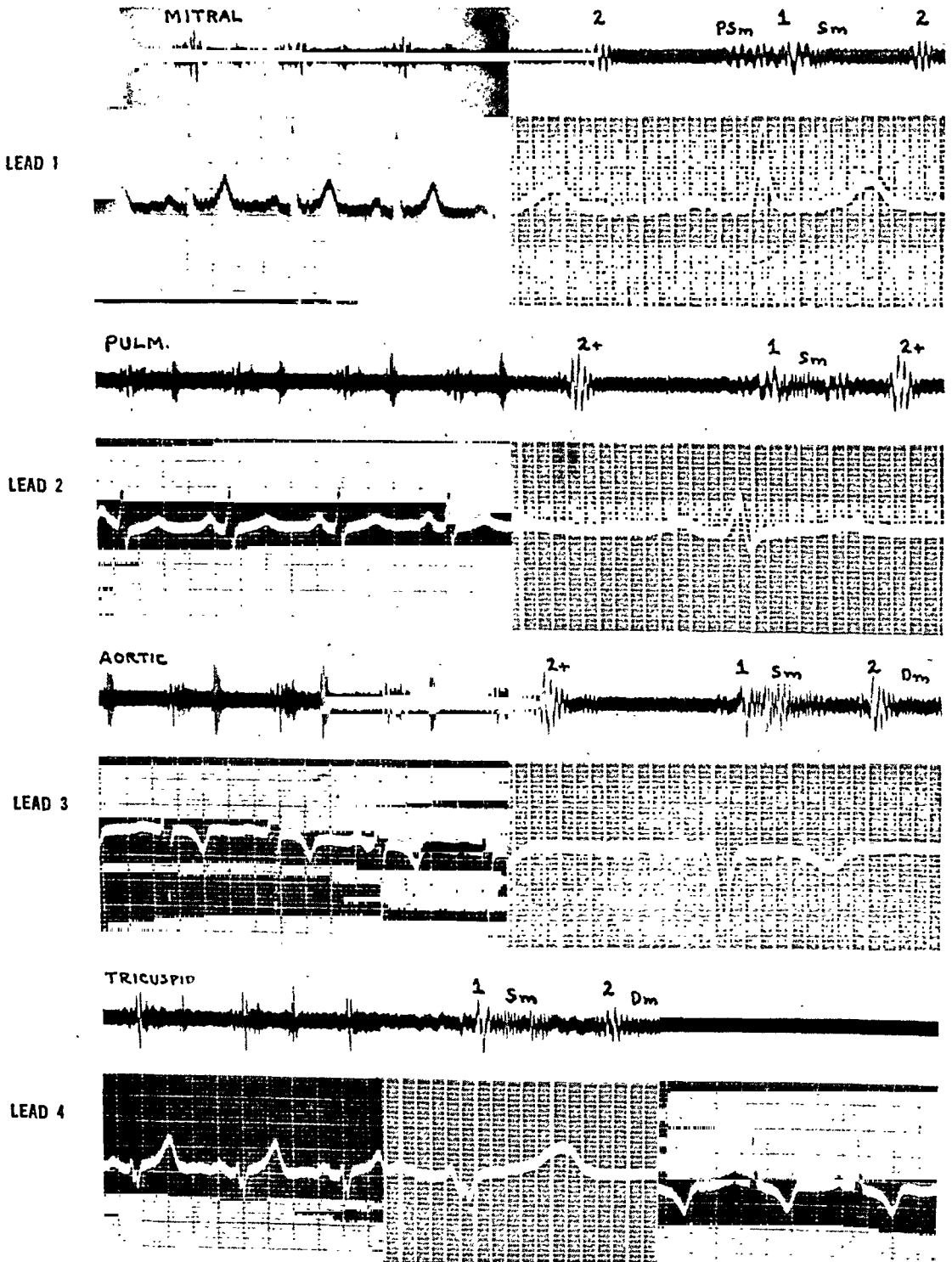
FIG. 3. Case 3.

could not be heard with the acoustic stethoscope but was easily recognized with the aid of an amplifying stethoscope. This murmur was too low pitched to be recognized clinically, being in the neighborhood of 50 vibrations per second. The systolic

murmur, of about 100 vibrations per second, was easily heard. The electrocardiogram revealed reciprocal S–T interval and T-wave changes in Leads I and III with left axis deviation; chest leads suggesting coronary disease with, possibly, an old occlusion.

Case 4. White female, aged 53, on December 2, 1939, complained of progressive dyspnea on exertion, palpitation and vertigo during the previous six months. After walking two blocks, choking spells with inability to get her breath, cough and weakness forced her to rest, the dyspnea lasting from one half to two hours. At times a sharp sticking precordial pain, lasting only a few minutes, occurred. She also complained that her fingers would turn blue and feel numb. Orthopnea, congestive failure, bilateral edema of the legs and thighs and distention of the abdomen were evident. The heart was irregular at the rate of 40 to 50 per minute. Blood pressure was 200 mm. Hg systolic and 114–110 mm. diastolic. The left heart border was at the anterior axillary line. Marked pulsation of neck vessels was noted. A loud systolic murmur was heard all over the precordium with a systolic thrill in the aortic area.

Stethogram (figure 4) showed a loud crescendo-decrescendo systolic murmur in all areas, emphasized in the aortic area and without normal heart sounds. The first sound in the mitral area had practically disappeared; the second sound was scarcely audible. The first sound in the pulmonic area was reduplicated and the second sound submerged in the systolic murmur which ran into a faint inaudible diastolic murmur. The aortic first sound was present but indistinct; the second sound was absent. The diastolic murmur noted in the pulmonic area was more distinct in the tricuspid area. The marked deformity and obliteration of heart sounds in complete heart block, which so often make it impossible to differentiate a systolic from a diastolic murmur, are well illustrated. Gross distortion of heart sounds is associated with organic not functional murmurs. A stethogram simplifies interpretation.

Case 5. White female, aged 30, on April 19, 1937, complained of progressive shortness of breath of three years' duration. She had had scarlet fever, repeated sore throats, diphtheria and influenza as a child. During the "influenza" she had "aches in her joints" but no other history suggesting rheumatic fever.

She appeared chronically ill, undernourished and weak. Pulse was 100 and regular. Blood pressure was 100 mm. Hg systolic and 74–70 mm. diastolic. Mucosa was pale. Skin was dry. There was slight bilateral ankle edema. The heart was slightly enlarged to right and left. The apex beat in the fifth interspace was just outside the left midclavicular line. A presystolic mitral thrill with long presystolic murmur was noted. The diagnosis was rheumatic heart disease with mitral stenosis. A typical mitral stenosis sound track is seen (figure 5) with large P_2, notched P_3, significant T-wave changes, and a tendency to right axis deviation in the electrocardiogram. The second sound in the mitral area is scarcely visible. The pulmonic second sound is only slightly accentuated. The record coincides with a sketch, previously made, of the heart sounds. Stethography is an invaluable aid in teaching the student to recognize, differentiate and readily to correlate the various sounds heard over the heart. It serves as a constant check on clinical findings.

Case 6. White male, aged 45, when first seen October 24, 1929, complained that heart trouble followed quinsy 20 years before with progressive shortness of breath, swelling of the ankles, cough and nausea during the previous four weeks. Rheumatic fever was not otherwise suggested.

He was acutely ill. The cervical veins were distended and pulsating irregularly. Ears, lips and fingers were cyanotic. The left heart border was 6 cm. beyond the midclavicular line, the right border 4 cm. to the right of the right sternal edge. Apex beat was seen and felt in the sixth interspace at the midaxillary line. An apical pre-
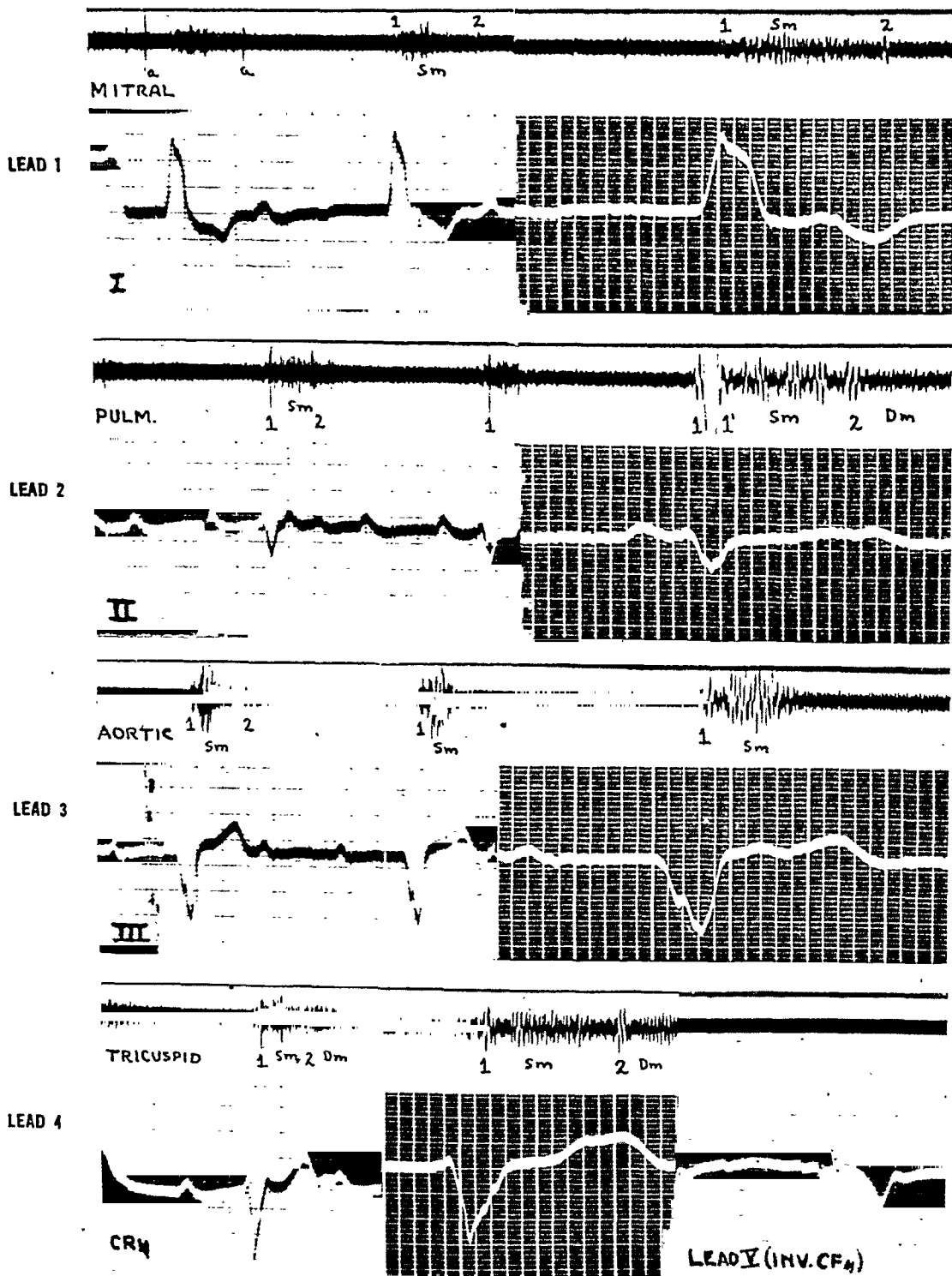
FIG. 4. Case 4.

systolic thrill was felt. The pulmonic second sound was accentuated. The liver edge was 3 cm. below the costal margin. Pulse was irregular at 70 to 80 per minute. Blood pressure was 150 mm. Hg systolic and 105–100 mm. diastolic. Reduplication
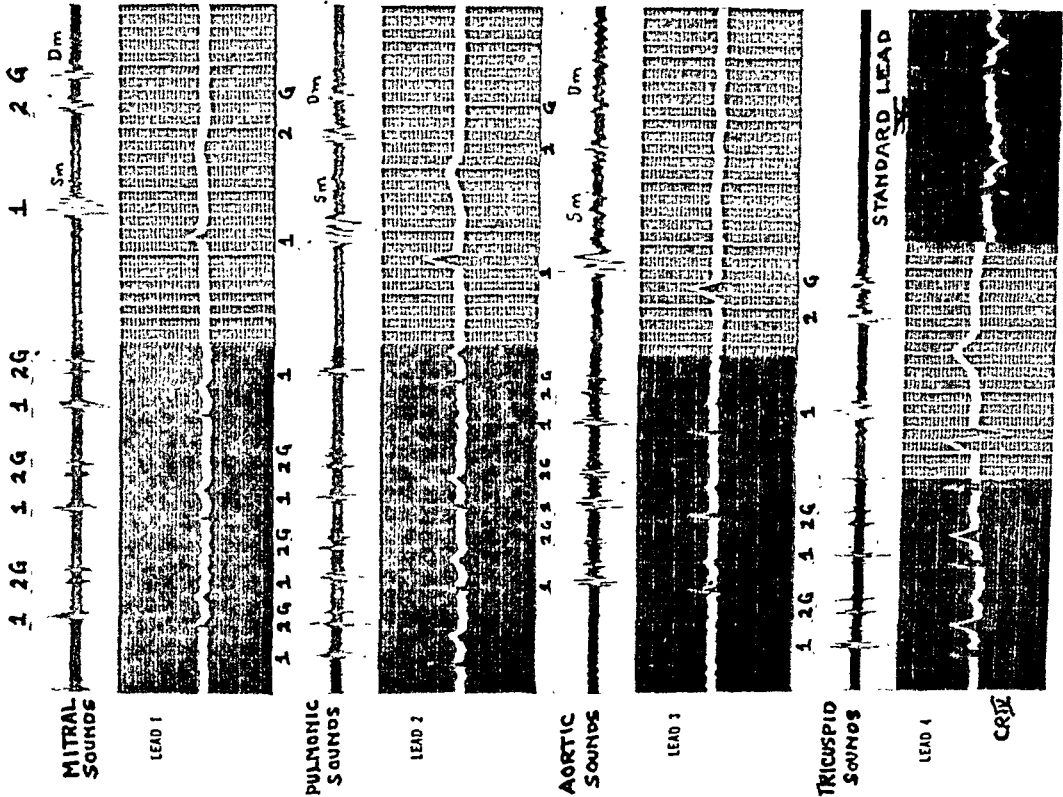
FIG. 6.   Case 6.
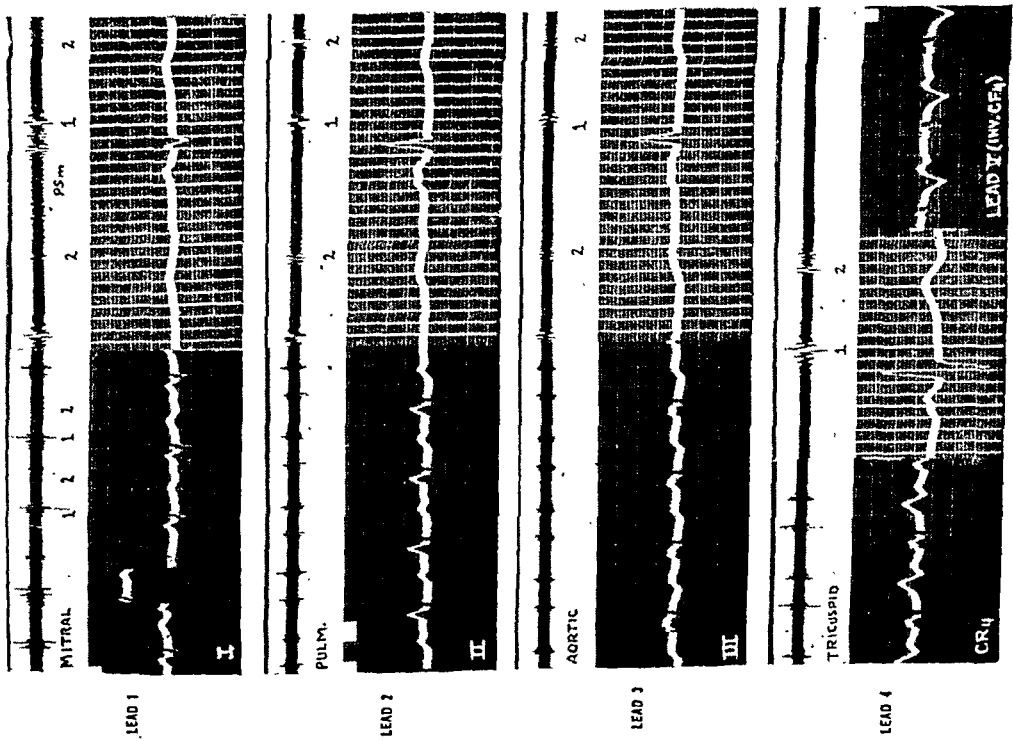
FIG. 5.   Case 5.

of the second sound, heard at the apex, was considered to be either a gallop rhythm or the opening snap of a mitral stenosis.

The electrocardiogram shows auricular fibrillation. The stethogram reveals a protodiastolic gallop rhythm (figure 6). Previous sound curves, without synchronized electrocardiograms, failed to show the true nature of this third sound. A systolic and diastolic murmur is present. A prominent auricular sound is seen in the mitral area.

DISCUSSION

We have correlated the clinical, electrocardiographic, stethographic and cardioscopic findings and conclude that the method is an invaluable aid in the early diagnosis and detection of heart disease. The method is simple, economical, and gives precise information unobtainable by other means. The diagnostic technic is readily applicable to the routine examination of recruits, to the routine screening of large populations, and to bedside and consultation practice. This practical and useful diagnostic aid undoubtedly will reveal many early cases of heart disease. At present there seems to be little excuse for avoiding the use of graphic methods in the study of heart disease. They increase accuracy in diagnosis. Due to limitations of hearing, it is well that our auditory acuity can be checked and rechecked. Serial changes in stethograms and electrocardiograms occur in acute coronary occlusion, coronary sclerosis, active rheumatic endocarditis, subacute bacterial endocarditis, patent ductus arteriosus, as well as in obesity, hypertension and anemia. In more than half of our cases the electrocardiogram gave valuable information; in more than one-third of the cases the stethogram was helpful. . Hence, it is reasonable to conclude that these graphic methods were of definite value in three out of four cases examined. The value of combined graphic methods in the diagnosis of heart disease is emphasized by the fact that the original Wassermann test was but 80 per cent efficient in detecting syphilis. With improvement in equipment, technic may be further simplified, and with more training and experience, interpretation of findings so improved, that more frequent recognition may prevent much of the damage now resulting from unrecognized rheumatic and coronary heart disease.

CONCLUSIONS

1. Combined graphic and cardioscopic diagnosis in conjunction with the routine clinical examination constitutes a practical plan for the early recognition of heart disease.

2. The results of combined electrocardiography, stethography and cardioscopy in the examination of 1108 cases of heart disease are reported and discussed.

3. A simplified chest lead technic is described. Chest lead abnormalities occurred in 29 per cent of the cases. These abnormalities were directly proportional to the age of the patient, being found in 20 per cent of those

between 31 and 41 years of age, and in 47 per cent of those between 61 and 87 years of age.

4. Organic heart murmurs are usually associated with heart sound abnormalities and often with changes in the electrocardiogram. Graphic methods are of value in differentiating organic and functional murmurs.

5. A diastolic murmur may be confused with a systolic murmur when the first heart sound is inaudible.

6. A stethogram is essential for the accurate diagnosis of gallop rhythm.

7. A stethogram differentiates a presystolic murmur from a "roughened" first sound.

8. In 88 per cent of 1108 cases clinical findings coincided with graphic findings.

9. In 12 per cent of 1108 cases the stethogram was essential for the diagnosis of gallop rhythm, of early mitral stenosis or of early aortic disease.

10. Of 102 cases of gallop rhythm, 42 per cent were misjudged clinically so far as timing the extra sound was concerned.

11. A double-beamed cardioscope for the instantaneous visualization of stethogram and electrocardiogram is predicted as a diagnostic adjunct in the rapid examination of recruits, applicants for flight training, insurance and in screening for unrecognized heart disease.

12. Six typical cases are reported. Results of clinical examination, correlated with graphic findings, demonstrate the value of the method for the early diagnosis of heart disease.

13. Serial stethograms, like serial electrocardiograms, are useful in following the course of heart disease. A comparison of records from the same patient or from other cases with the same disease is frequently of value.

14. Cardioscopy as well as combined stethography and electrocardiography aids in teaching, since visual impressions are always superior to verbal descriptions.

15. This method of diagnosis is young but it will grow. Stethography has already arrived at a stage comparable to electrocardiography during the third decade of its development.

BIBLIOGRAPHY

1. MACKENZIE, J.: Diseases of the heart, First Edition, 1908, Oxford University Press, London, p. 5.
2. BARTLETT, W. M., and CARTER, J. B.: Combined electrocardiography, stethography and cardioscopy in the selection of pilots, Jr. Aviation Med., 1941, xii, 1.
3. RAPPAPORT, M. B., and SPRAGUE, H. B.: Physiologic and physical laws that govern auscultation, and their clinical application, Am. Heart Jr., 1941, xxi, 257.
4. MANNHEIMER, E.: Calibrated phonocardiography, Am. Heart Jr., 1941, xxi, 151.
5. ARENBERG, H.: Phonocardiography and its clinical application, ANN. INT. MED., 1941, xiv, 1607.
6. YLVISAKER, L. S., and KIRKLAND, H. B.: The significance of the position of the subject in the evaluation of the electrocardiogram, Am. Heart Jr., 1940, xx, 592.

7. SCHERF, D., and WEISSBERG, J.: The alterations of the T-waves caused by a change of posture, Am. Jr. Med. Sci., 1941, cci, 693.

8. CARTER, J. B.: A simplified chest lead technique for routine clinical use. (To be published.)

9. ROTH, I. R.: On the use of chest leads in clinical electrocardiography, Am. Heart Jr., 1935, x, 798.

10. CARTER, J. B.: Graphic changes of coronary occlusion, Ill. Med. Jr., 1941, lxxx, 485–500.

11. ORIAS, O., and BRAUN-MENENDEZ, E.: The heart sounds in normal and pathological conditions, 1939, Oxford University Press, London.

12. WIGGERS, C. J.: Physiology in health and disease, Third Edition, 1939, Lea and Febiger, Philadelphia.

13. BOYER, N. H., ECKSTEIN, R. W., and WIGGERS, C. J.: Characteristics of normal heart sounds recorded by direct methods, Am. Heart Jr., 1940, xix, 257.

14. PAZZANESE, D.: A Fonocardiografia, 1940, Prefeitura do Municipio de Sao Paulo, Sao Paulo.

15. GOODMAN, M. J.: Paroxysmal flutter of the diaphragm simulating coronary occlusion, Jr. Am. Med. Assoc., 1941, cxvi, 1635.

SYNDROME OF RUPTURE OF AORTIC ANEURYSM INTO THE PULMONARY ARTERY; REVIEW OF THE LITERATURE WITH REPORT OF TWO CASES *

By Richard E. Nicholson, B.S., M.D., *Dallas, Texas*

The incidence of rupture of an aortic aneurysm into the pulmonary artery is of rare enough occurrence to warrant publication by most clinicians of their respective cases soon after discovery. Even rarer is the antemortem diagnosis of such a condition, because the diagnostician is either unfamiliar with the syndrome or discards the possibility in favor of a more statistical probability.

The terminology "arteriovenous" aneurysm or anastomosis with reference to the great vessels leaving the heart is not preferable. Although it is true that with regard to the circulating blood in a communication between pulmonary artery and aorta there is a mixing of arterial and venous blood, it is the general consensus of opinion that the term "vein" must adhere to two fundamentals: a carriage of unoxygenated blood and a return of this blood to the heart. Since the communication between the two vessels involved here follows only one of these principals, i.e., the carriage of unoxygenated blood, and is technically an artery since it carries blood away from the heart, we are of the opinion that "arterio-arterial anastomosis" or "arterio-arterial aneurysm" is more applicable to the condition of the shunt of blood from an aneurysm of the aorta into the pulmonary artery.

Since the diagnosis of a rupture of an aortic aneurysm into the pulmonary artery is based upon several essential and definite criteria, all of which are quite obvious and easily discernible to even the most inexperienced, it is only necessary to call attention to the existence of such a syndrome in order to simplify a diagnosis. Such is the purpose of this paper.

HISTORY

That such an "arterio-arterial" aneurysm is indeed uncommon is evidenced by the fact that there exist in the literature only 81 cases, including clinical, autopsy reports, and museum specimens. As White[61] stated in a recent article, the majority of the patients reported are to be found in the past century. A total of 54 have been mentioned in the literature from 1812–1900. During the past 41 years only 27 have been published, and of these only four have been diagnosed antemortem (Scott,[48] 1924; White,[61] 1941; Porter[40] (2 cases), 1941). Two more were correctly diagnosed at

the Charity Hospital of Louisiana in New Orleans in 1941. Wade [57] recognized one case before death in 1861.

Probably the earliest account of an aortic aneurysm rupturing into the pulmonary artery is one related in the Bulletin de la Faculté de Médicine de Paris in 1811 by Drs. Payne and Zink in which the sac is supposed to have "s'ouvrant" into the pulmonary artery. Peacock,[37] however, states that in this case it only appears to have projected into the vessel and not to have communicated directly with it. For that reason this case was eliminated in this analysis. In 1812, Wells [59] recorded a case seen by Baillie in which such a rupture occurred. Munro [22] in 1839 described a patient with an "arterio-arterial" aneurysm and in 1840, Reid [43, 44, 45] added three more cases to the sparse literature: two with ruptures into the main trunk of the pulmonary artery and one between the descending aorta and the left pulmonary branch. This latter case is of interest in that the author states that the site of communication corresponded exactly with the site of the fetal ductus arteriosus. This brings up the controversial subject of congenital origin versus a communication resulting from a ruptured aneurysm. Thurman [55] in 1840 reviewed the reports of spontaneous varicose-aneurysms of the ascending aorta and discussed five instances of communication between the pulmonary artery and aorta. In 1868 Peacock [37] summarized the literature and was able to find 19 patients with this type of communication. Since that time, reports of this syndrome have emerged in the literature at intervals with occasional surveys. In 1907 Kappis [24] in Germany reviewed 32 cases and added one of his own. Among the first patients reported in this country was one by Hollis [20] in 1908. This was quickly followed by other reports from different medical centers of the United States. The latest were those of White,[61] Porter,[40] and Mallory.[33]

In reviewing the literature it was found that the majority of the reports were in the English journals, with only 11 in the German literature, three in the French, and one in the Portugese (Brazilian), and one in Spanish (Argentine).

INCIDENCE

General Incidence from the Literature. As mentioned above only 81 cases have been reported in the literature. The patients from Charity Hospital bring the total to 83. The close relationship between the two great vessels offers ample opportunity for communication between them, and considering the frequency of aneurysms of the ascending and transverse aorta, one wonders at the low incidence of rupture into the pulmonary artery. The possibility that this occurs more frequently than is reported is probably explained by the failure to recognize this condition clinically, the neglect on the part of the pathologist to open the pulmonary artery unless clinical evidence so indicates, and lastly the possibility of leaking or pinpoint communication which even the most diligent and scrupulous inspection may fail to reveal.

A factor which might likewise tend to account for the low occurrence of such a communication, even in the face of the close anatomical relationship, is the more frequent occurrence of aneurysms of the ascending aorta in the anterior and right aspects of the vessel rather than in the left and posterior parts.[4]

From a review of the literature in the 65 patients reported in which the sex was stated, the occurrence in males was 59 cases, 91 per cent, as contrasted to that of only six females, 9 per cent. This is probably explained upon the basis of greater frequency of aneurysms in males and upon the more prevalent amount of physical strain to which the male is exposed.

Boyd[4] in a perusal of 4000 thoracic aneurysms found only 45 communications between the aorta and the pulmonary artery, an incidence of 3.7 per cent of all points of rupture. Lemann[29] found a closely allied percentage, 3.04 per cent of 592 selected cases from the literature. However, in a review of 2000 case records at the Charity Hospital between the years 1905 and 1914, he found only 52 thoracic aneurysms with 11 ruptures and none into the pulmonary artery. Delp[10] of the University of Kansas, in 6099 autopsies (of which there were 85 thoracic aneurysms), found only one instance.

Incidence at the Charity Hospital of Louisiana in New Orleans. From the records of the Charity Hospital (table 1) only two were found between June 30, 1911, and December 31, 1941, which showed definite evidence of rupture of an aortic aneurysm into the pulmonary artery. There was one case in which a communication between the two vessels resulted from an aneurysm of the left pulmonary branch that ruptured into the aorta. This case is not included in this analysis.

During the period between 1911 and 1941 there were 1,052,667 hospital admissions and approximately 23,239 autopsies. The total number of aneurysms of the aorta in this interval was 1393 and of this 219 were of the thoracic aorta. During this period 110 of the 219 thoracic aortic aneurysms ruptured (table 1). Thus the incidence in 30 years of rupture of an aortic aneurysm into the pulmonary artery in this survey is about 0.91 per cent of all thoracic aortic aneurysms, and 1.83 per cent of all ruptured thoracic aortic aneurysms.

PATHOLOGY

Anatomical Considerations. The anatomical relations of the aorta and pulmonary artery are such that all three parts of the thoracic aorta are in contact with the pulmonary artery or its branches as far as the middle part of the descending thoracic aorta. At its origin from the conus arteriosus of the right ventricle, the pulmonary artery extends obliquely upward and backward, passing at first in front of and then to the left of the ascending aorta. At the under surface of the arch, the pulmonary artery divides into right and left branches, the right passing posterior to the ascending trunk and the left passing anterior to the descending trunk of the aorta.

TABLE I

Incidence of Rupture of Aortic Aneurysms (Thoracic and Abdominal) Over a Period of 30 Years (1911–1941) from 1,393 Cases of Aortic Aneurysm at The Charity Hospital of Louisiana at New Orleans

Portion of Aorta Involved	Aneurysm Rupturing into:	Number	Percentage	
			Of Total Thoracic Aneurysms	Of Total Abdominal and Thoracic Aneurysms
Thoracic Ascending				
	Esophagus	2	1.8	1.4
	Right bronchus	4	3.6	2.9
	Left bronchus	3	2.7	2.1
	Pericardium	9	8.2	6.4
	Trachea	4	3.6	2.9
	Right pleural cavity	2	1.8	1.4
	Left pleural cavity	4	3.6	2.9
	Right lung	1	0.9	0.7
	Pulmonary artery	1	0.9	0.7
	Total	30	27.1	21.4
Transverse				
	Esophagus	11	10.0	7.9
	Left bronchus	4	3.6	2.9
	Pericardium	3	2.7	2.1
	Trachea	6	5.5	4.3
	Right pleural cavity	3	2.7	2.1
	Left pleural cavity	10	9.1	7.1
	Left lung	1	0.9	0.7
	Right lung	2	1.8	1.4
	Externally	2	1.8	1.4
	Pulmonary artery	1	0.9	0.7
	Total	43	39.0	30.7
Descending				
	Esophagus	7	6.4	5.0
	Left bronchus	3	2.7	2.1
	Trachea	1	0.9	0.7
	Right pleural cavity	5	4.5	3.6
	Left pleural cavity	16	14.5	11.4
	Aorta (dissecting)	1	0.9	0.7
	Right lung	2	1.8	1.4
	Mediastinum	1	0.9	0.7
	Peritoneum	1	0.9	0.7
	Total	37	33.5	26.3
	Total Thoracic	110		78.4
			Of Total Abdominal Aneurysms	
Abdominal				
	Peritoneum	14	46.7	10.0
	Retroperitoneal space	12	40.0	8.6
	Left pleural cavity	3	10.0	2.1
	Right pleural cavity	1	3.3	0.7
	Total	30		21.4
Total Ruptured Aortic Aneurysms		140		

As mentioned above, this close relationship of the pulmonary artery and the ascending, transverse, and upper part of the descending aorta offers ample opportunity for communication between the two. This anatomical consideration is important in that even with this close approximation of the two great vessels added to the frequency of aortic aneurysms in these areas, rupture into the pulmonary artery occurs in only a very small percentage of cases. Some explanation of this has been mentioned above.

Site of the Aneurysm. Boyd[4] has referred to the more frequent occurrence of aneurysms of the ascending aorta upon the anterior and right aspects of the vessel rather than upon the posterior and left. In the latter site the sac would be in close approximation to the pulmonary artery. In the arch of the aorta the greater frequency of occurrence is in the inferior

TABLE II

Incidence of Site of Rupture of Aneurysm of the Thoracic Aorta from Three Selected Studies and One from The Charity Hospital. (Modified from Delp.)

	Delp[10]	Lemann[29]	Boyd[4]	Charity Hospital
No. of Autopsies	6,099	2,000	*	23,239
No. of Thoracic Aneurysms	85	52	4,000	219
No. of Ruptured Aneurysms	46	11	1,197	110
Rupture Site:				
Pericardium	28	2	369	12
Left thorax	13	1	174	30
Right thorax		1	88	10
Bronchial tree	1	3	171	25
Esophagus	1	3	112	20
Pulmonary artery	1	—	45	2
Superior vena cava	—	—	44	—
Mediastinum	3	—	20	1
Externally	1	—	61	2
Right lung	—	—	12	5
Left lung	—	1	40	1
Miscellaneous	1	—	61	2

* Only selected thoracic aneurysms.

and posterior regions of the vessels.[4] The explanation of this is not well understood, but one may postulate the formation of an aneurysmal sac along the lines of least resistance.

Boyd[4] states that the frequency of occurrence of aneurysm of the aorta is in the relation of 10 in the ascending, seven in the arch, three in the descending, and one in the lower thoracic aorta. Lemann[29] from his series of cases found the arch to be the most frequent site with the descending next and the ascending last. In the series of cases of ruptured aneurysm at Charity Hospital (table 1) between 1911–1941, the incidence was higher in the arch, 30.7 per cent, with 26.3 per cent in the descending, 21.4 per cent in the abdominal, and 21.4 per cent in the ascending aorta.

However, a review of the reports in the literature of rupture of an aortic aneurysm into the pulmonary artery indicates that the majority communicated through a rupture of an aneurysm of the first part of the thoracic aorta (tables 3 and 4). Of the reported cases (74) in which the site of the

TABLE III

Cases of Rupture of an Aortic Aneurysm into the Pulmonary Artery, From a Review of the Literature.
A total of 81 cases has been mentioned in the literature since 1812, including museum specimens.

Case	Age	Sex	Syphilis	Onset	Appearance	Dyspnea	Cough	Edema	Pain in Chest	Pulse	Murmur	Thrill	Roentgen-Ray and E.K.G.	Site of Aneurysm	Duration	Autopsy
1. Wells [32]	53	M	?	Sudden onset after walking and playing with children. 3 yrs. cardiac disease	—	—	—	—	—	—	—	—	—	1st part of descending aorta. Size of orange	8-9 hrs.	Aorta adhered to pulmonary artery. Ragged opening ⅓ in. long in aorta communicating with pulmonary artery.
2. Thurman [33]	33	M	—	Sudden while lifting a heavy load. Giving away in chest	Face pale, lips vivid	Marked dyspnea	Cough with visco-sanguinous sputum	Lower extremities	Pain in chest extending to spine	Jerking pulse	Continuous sawing in 2nd left interspace	Purring tremor at 2nd left interspace	—	1st part ascending aorta	11 wks.	Aneurysm projected into mouth of right ventricle and into pulmonary artery. Two openings between aorta and pulmonary artery.
3. Reid [43] Case 1	36	M	—	No history of onset. Cardiac symptoms for six months	—	—	—	—	—	—	—	—	—	1st part descending aorta	Died soon after admission	Opened into pulmonary artery (left) by rounded, smooth edged aperture. Not believed to be a reopened ductus arteriosus.
4. Reid [44] Case 2	60	M	—	Sudden onset. General cardiac symptoms previously	—	—	—	—	—	—	—	—	—	Ascending aorta. Size of orange	Few hours	Pressed on left auricle. Opened into pulmonary artery by a long tear 1.3 in. in length.
5. Reid [45] Case 3	53	M	—	Sudden onset. Bronchial symptoms for several months	—	Marked dyspnea. Loss of consciousness	—	—	—	—	—	—	—	Ascending aorta. Size of fist	4 mins.	Opened into pulmonary artery by a ragged fissure 1½ in. long.
6. Turnbull [38]	41	M	—	Sudden onset following a fall	—	—	—	—	—	—	Continuous murmur	Purring tremor at base	—	Ascending aorta above valves	5 mo.	One opening into pulmonary artery and one into right ventricle.
7. Munro [22]	24	M	—	Sudden onset following pneumonia	Tumid and livid	Marked dyspnea and palpitation	Cough and expectoration	Abdomen and lower extremities extending to anasarca	—	"Large thrilling"	Continuous over whole chest	—	—	Ascending aorta	10 wks.	Two openings into pulmonary artery.

* indicates those instances diagnosed before death.

+ under the column labeled "Syphilis" indicates the presence of syphilis in the patient.

+? indicates questionable syphilis.

Table III—Continued

Case	Age	Sex	Syphilis	Onset	Appearance	Dyspnea	Cough	Edema	Pain in Chest	Pulse	Murmur	Thrill	Roentgen-Ray and E.K.G.	Site of Aneurysm	Duration	Autopsy
8. Smith[50]	22	M	—	Sudden onset with vertigo and syncope	Face pale, lips cyanotic	Orthopnea and palpitation	—	Edema of face	Precordial pain	Intermittent	Systolic murmur	Intense over whole chest	—	1st part ascending aorta	4 mo.	Small opening into pulmonary artery with rounded edges.
9. Rokitansky[47] Case 1	41	M	—	—	—	—	—	—	—	—	—	—	—	Ascending aorta. Size of walnut	Sudden death	Opened by triangular aperture with ragged edges into pulmonary artery.
10. Rokitansky[47] Case 2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	Opening into pulmonary artery.
11. Rokitansky[47] Case 3	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	Communication between aorta and right pulmonary artery.
12. Rokitansky[47] Case 4	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	Communication between aorta and right pulmonary artery.
13. Rokitansky[47] Case 5	—	—	—	Sudden onset in cardiac condition	Face pale, lips cyanotic	Marked dyspnea, palpitation	Cough with hemoptysis	—	—	Jerking	Systolic in 3rd left interspace	Thrill in systole	—	Ascending aorta. Size of hen's egg	2 mo.	Communication between aorta and right pulmonary artery.
14. Ogle[38]	27	F	—	Sudden onset following vomiting	—	—	—	—	—	—	—	—	—	Arch and descending aorta	1–2 hours	Aperture size of quarter opening into pulmonary artery.
15. Herapath[18]	53	M	—	Sudden. "Giving away in chest"	—	Marked dyspnea	Cough and hemoptysis	Anasarca	Chest pain at onset	Irregular	Continuous blowing murmur	—	—	1st part ascending aorta. Size of walnut	5 mo.	Lacerative aperture 1 in. long connecting aorta with pulmonary artery.
16. Bennett[3]	33	M	—	Sudden onset with pain in chest	—	—	—	—	—	—	—	—	—	Ascending aorta	1 yr.	Transverse communication between aorta and pulmonary artery.
17. Pierceson[39]	61	M	—	Sudden onset following exertion	Lividity of face and lips	Orthopnea	—	Lower extremities	Onset with pain in chest	Corrigan	Systolic murmur	Tremor in 2nd left interspace	—	—	—	Bilocular aneurysm 3 cm. above aortic valves. Small communication between aorta and pulmonary artery.
18. Wade*[57]	35	M	—	—	—	Dyspnea	Cough. Hemorrhage from rectum	—	—	—	Double murmur in upper left chest	Purring, tremor in upper left chest	—	1st part ascending aorta. Size of hen's egg	2 mo.	Communication with pulmonary artery via a slit "3 lines long." Smooth, rounded aperture. Second opening into right ventricle.
19. Roberts[46]	28	M	—	Sudden onset. Signs of cardiac disease	Lips livid, face pale	Orthopnea	Cough and hemoptysis	Legs, thighs, ascites	—	Quick, jerking	Continuous murmur	Continuous thrill	—	1st part ascending aorta	2 mo.	Funnel shaped aneurysm. Communication between vessels size of a pea.

TABLE III—Continued

Case	Age	Sex	Syphilis	Onset	Appearance	Dyspnea	Cough	Edema	Pain in Chest	Pulse	Murmur	Thrill	Roentgen-Ray and E.K.G.	Site of Aneurysm	Duration	Autopsy
20. Peacock[37]	26	M	—	Sudden onset with epigastric pain	Lips livid, cheeks flushed	Increasing dyspnea	Cough	Anasarca	Intense pain in epigastrium	Corrigan	Double murmur	—	—	1st part ascending aorta. Size of large hen egg	2 mo.	Smooth orifice "2 lines wide and 4 lines long." Evidence of erosion and not sudden rupture.
21. Taylor[53]	30	M	—	Gradual onset during bad weather	Jaundice	Orthopnea	—	Lower extremities and ascites	Pain in chest at onset	Rapid but, not collapsing	Double murmur at 2nd left interspace	Systolic	—	Ascending aorta, size of large walnut	48 hrs.	Communication between vessels by way of a long rent ½ inch in length.
22. Taylor[54] Case 1	30	M	—	Sudden onset after severe vomiting	"Negroid" appearance	—	—	—	Pain in precordial area	Scarcely perceptible	—	—	—	Arch of aorta	2 hrs.	Small area of communication between aorta and pulmonary artery.
23. Taylor[54] Case 2	45	M	—	Sudden onset with fluttering in left hypochondrium	Face and lips pale. Slight malar flush	Inspiratory dyspnea (oliguria)	Cough with hemoptysis	Anasarca	Pain in epigastrium	—	Systolic at 2nd left interspace	Systolic thrill in 2nd left interspace	—	Ascending aorta	8 wks.	Small aperture with smooth rounded edges between aorta and pulmonary artery.
24. Taylor[54] Case 3	44	M	+	Sudden onset with severe symptoms	"Dusky" face, congestion of lips	Dyspnea	Cough	Anasarca	Severe precordial pain 2 yrs. prior to admission	Corrigan	To and fro murmur down sternum	—	—	Ascending aorta. Size of fetal head	2 yrs. (5 days after admission)	Main sac had 2 secondary pouches, one of which opened into the pulmonary artery through a small aperture.
25. Taylor[54] Case 4	?	M	+	Sudden onset with weakness	Livid face	Dyspnea	Slight cough with hemoptysis	Lower extremities	Pain over precordium	Feeble pulse	Double murmur in 2nd-3rd left interspaces	Systolic	—	Ascending aorta	9 mo.	Adhesion of pulmonary valves to aneurysm. Communication between aorta and pulmonary artery through a smooth edged aperture 5 mm. in diameter.
26. Taylor[54] Case 5	40	M	+?	Sudden onset while lifting hides	Lividity of face and lips	Dyspnea	Cough with hemoptysis	Anasarca	Pain in precordium	Corrigan	Systolic in left 3rd-4th interspaces	Systolic in left 2nd-3rd interspaces	—	Ascending aorta	12 mo.	Aneurysm separated from pulmonary artery by thin septum which is beginning to rupture—a leaking aperture.
27. Taylor[54] Case 6	45	M	—	Sudden onset 3 wks. after hard labor	Lividity	Dyspnea	Cough with muco-purulent sputum	Lower extremities	Pain in left chest	Corrigan	Roaring musical bruit at base. Continuous	No thrill	—	Ascending aorta	4 mo.	Small opening 2½ mm. in diameter opening into pulmonary artery.
28. Taylor[54] Case 7	43	M	+	Gradual with cardiac signs	Pallor	Great dyspnea (oliguria)	—	Anasarca	Tightness in chest	Regular and compressible	Systolic	—	—	Ascending aorta	? 6 yrs. (4 days after admission)	Opened into pulmonary artery by one old aperture and one recent rupture; third opening doubtful.

TABLE III—Continued

Case	Age	Sex	Syphilis	Onset	Appearance	Dyspnea	Cough	Edema	Pain in Chest	Pulse	Murmur	Thrill	Roentgen-Ray and E.K.G.	Site of Aneurysm	Duration	Autopsy
29. Murchison [23]	48	M	—	Sudden onset after severe fall	Extreme lividity of face. Body pale	Dyspnea (palpitation, euphoria)	Cough	Anasarca	No pain	Feeble but regular	Systolic "bellows like" over whole chest	—	—	Ascending aorta	7 mo.	Communicated with pulmonary by circular aperture 1¼ in. above valves.
30. Cayley [6]	37	M	—	Sudden onset; no precipitating factor	Great lividity	Dyspnea	—	Legs and ascites	Severe pain in left chest	Corrigan	Double "bellows" murmur 2nd interspace	—	—	Ascending aorta. Size of walnut	1 mo.	Communicated with pulmonary artery through a smooth rounded orifice 1¼ in. in diameter.
31. West [60]	38	M	—	Sudden onset	—	Dyspnea	Cough	—	Severe in left chest	—	Double in 3rd-4th left interspaces	Coarse thrill left 3rd-4th interspaces	—	Ascending aorta. Size of egg	10 wks.	Communication between aorta and pulmonary artery via aperture ½ in. in diameter.
32. Hanford [16]	35	M	—	Sudden onset	—	Orthopnea	Cough, abundant frothy sputum	Lower extremities	Precordial pain	Irregular, small, feeble, fluttering	Harsh systolic at 3rd left interspace	Systolic in 3rd left interspace	—	Ascending aorta	—	Communication between aorta and pulmonary artery through aperture size "three-penny piece."
33. Lamplough [28]	27	F	+	Sudden onset while climbing stairs	Face pale, lips livid	Orthopnea	Cough and hemoptysis	Anasarca	Pain across chest and between shoulders	Corrigan	Continuous murmur in 2nd interspace	Prolonged systolic in 2nd, 3rd, 4th left interspaces	—	Ascending aorta. Size of pullet's egg	4 mo.	Communication between aorta and pulmonary artery via 2 small rounded orifices.
34. Gairdner [15] Case 1	42	M	+?	The patient was a blacksmith. No clinical history is given. The aneurysm was on the ascending aorta, about the size of a chestnut, and projected directly against and pushed into the first part of the pulmonary artery rendering the vessel convex. There was an oval aperture connecting the two vessels, the margins of which were well rounded.												
35. Gairdner [15] Case 2	31	M	—	—	Lividity	Dyspnea (oliguria)	—	Anasarca	Great pain in precordium	Irregular. Of low tension	Double murmur	—	—	Ascending aorta. Size of fist	1 yr.?	Communication between aorta and pulmonary artery through an oval aperture 1 cm. long. Orifice had well rounded edges.
36. Gairdner [14] Case 3	35	M	—	Sudden onset	Slight pallor	Orthopnea (euphoria, oliguria)	Cough	Anasarca	None	Corrigan	Continuous murmur to left of sternum	Thrill to left of sternum	—	Ascending aorta	—	Small communication between aorta and pulmonary artery. Right heart enlarged.
37. Clarke [7]	36	M	+?	Sudden onset	"Slight dusky color"	Orthopnea (euphoria, oliguria)	Cough	Anasarca	None	Not of Corrigan type	Continuous in 2nd and 3rd left interspaces	Continuous 2nd-3rd left interspaces	—	Ascending aorta	·?	Small communication between aorta and pulmonary artery. Right heart enlarged.
38. Smith [49]	31	M	+?	Sudden onset while on bedpan	Face and lips blanched	Orthopnea	Cough	Upper part chest; neck and head	Pain in chest radiating to neck and head	Absence of radial pulse	None	None	—	Ascending and transverse aorta. Size of orange	2 hrs.	Communication between aorta and pulmonary artery through a freshly torn aperture.

TABLE III—Continued

Case	Age	Sex	Syphilis	Onset	Appearance	Dyspnea	Cough	Edema	Pain in Chest	Pulse	Murmur	Thrill	Roentgen-Ray and E.K.G.	Site of Aneurysm	Duration	Autopsy
39. McNabb [34]	?	M	+ ?	Sudden following exertion	—	Dyspnea	Cough and vomiting	Anasarca	—	Rapid, forceful	Loud, rasping systolic murmur at 5th left interspace	—	—	Ascending aorta	77 days	Communicated with pulmonary artery through an aperture ¾ cm. in diameter.
40. Wooley [62]	40	M	+	Sudden onset	(Negro)	Dyspnea to orthopnea	Cough	Lower extremities and trunk	Pain in left chest	Corrigan	Harsh double murmur	—	—	Ascending aorta	4 mo.	Adherent to pulmonary artery. Communication between vessels through apertures. Edges smooth and rounded.
41. Korb [28]	53	M	?	Sudden onset while climbing stairs	Moderate cyanosis	Dyspnea	—	No edema	Epigastric pain	Barely palpable	Loud systolic murmur at pulmonic valve area	None	—	Ascending aorta	3 hrs.	Communication between aorta and left branch of pulmonary artery. Ragged aperture 8 cm. from pulmonary valve.
42. Stevenson [52] Case 1	—	M	+	Sudden onset	(Negro)	Dyspnea	Cough, hemoptysis	Ascites, extremities	Precordial pain	Corrigan	Continuous at pulmonic valve area	Continuous thrill	—	Arch of aorta	15 mos.	Two communications between aneurysmal sac and pulmonary artery. Each had smooth, rounded edges.
43. Stevenson [52] Case 2	20	M	+	Sudden after wiring of aneurysm	Lips and ears cyanotic. Mucous membranes pale	Dyspnea	Cough	Face and extremities	Pain in chest	Corrigan	Continuous machinery murmur in 3rd left interspace	Systolic thrill	—	Ascending aorta	4 wks.	Communication between vessels via aperture 6 mm. in diameter. Irregular edges.
44. Stevenson [52] Case 3	45	M	—	Sudden onset. Cold and cough present	(Negro) Pale mucous membranes	Dyspnea to orthopnea	Cough and expectoration	Legs, ankles; ascites	—	Regular but of low tension	Double murmur in 3rd left interspace	Thrill in carotid area	—	Ascending aorta	3 mo.	Communicated with pulmonary artery through a pin point aperture.
45. Scott [48] Case 1	51	F	+	Sudden onset	(Negro)	Dyspnea	—	Chest, ascites, lower part of body	—	Corrigan	Continuous in 2nd and 3rd left interspaces	Continuous in 2nd and 3rd left interspaces	Aorta normal. Heart enlarged in all directions. Wide at base of heart	Ascending aorta	2 mo.	Communication between aorta and pulmonary artery by a ragged edged aperture 3 by 6 mm.
46. Scott * [48] Case 2	29	M	+	Sudden onset while at work	(Negro)	Dyspnea	—	Lower extremities	—	Corrigan	Continuous in 2nd left interspace	Systolic thrill at 2nd left interspace	Heart slightly enlarged. No widening at base. Aorta not enlarged.	Ascending aorta	3 wks.	Communication between aorta and pulmonary artery through ragged edged aperture 1½ cm. in width.

Table III—Continued

Case	Age	Sex	Syphilis	Onset	Appearance	Dyspnea	Cough	Edema	Pain in Chest	Pulse	Murmur	Thrill	Roentgen-Ray and E.K.G.	Site of Aneurysm	Duration	Autopsy
47. Lenoble [30]	40	M	–	Sudden onset	(Negro) Sclerae jaundiced	Dyspnea	Cough	Anasarca	—	Irregular, compressible, small	Double murmur at 2nd left interspace	Systolic at 2nd left interspace	—	Ascending aorta	11 mo.	Smooth, rounded orifice size of lead pencil connecting aorta and pulmonary artery.
48. Clerc [8]	40	M	+	Sudden onset following pneumonia	Intense cyanosis	Dyspnea	Cough	Anasarca	—	Irregular	Systolic in 2nd left interspace	None	Enlarged aortic knob. Enlarged pulmonary conus	Ascending aorta	4 yrs.	Communication between aorta and pulmonary artery through an aperture 7 mm. in diameter. Edges smooth and rounded.
49. Potter [41]	53	M	+	Sudden onset following strenuous exertion	Lips moderately cyanotic	Dyspnea	Cough	Lower extremities	Precordial pain	—	Systolic murmur in 2nd and 3rd left interspaces	Systolic in 2nd and 3rd left interspaces	—	Ascending and transverse aorta	51 hrs.	Communication between aorta and pulmonary artery via an aperture 1.2 cm. long.
50. Delp [10]	40	M	+	Sudden onset while digging in cellar	(Negro)	Paroxysmal dyspnea	No cough	No edema	Substernal pain radiating to back	Corrigan	Harsh, continuous, machine-like murmur in 2nd left interspace	Systolic in 2nd left interspace	Prominent pulmonary conus. Heart enlarged. Aorta not enlarged. E.K.G.: Right axis deviation. Diphasic T₂, T₃. Sinus tachycardia 130/min. Sound tracings showed presence of continuous murmur at left base	Ascending aorta	48 hrs.	Communication between aorta and pulmonary artery (left branch of pulmonary artery) through a torn, lacerated aperture 2 cm. long.
51. Reeves [42] Case 1	36	M		Sudden onset	—	Dyspnea	Cough	Lower extremities	—	Slow pulse	Continuous murmur	—	—	Ascending aorta. Size of orange	6 mo.	Communication between aorta and pulmonary artery by a long slit.
52. Reeves [42] Case 2				Sudden onset and sudden death	No clinical symptoms observed	—			—	—	—	—	—	—	—	—
53. Reeves [42] Case 3			•	Sudden onset and sudden death	No clinical symptoms observed	—			—	—	—	—	—	—	—	—

TABLE III—*Continued*

Case	Age	Sex	Syphilis	Onset	Appearance	Dyspnea	Cough	Edema	Pain in Chest	Pulse	Murmur	Thrill	Roentgen-Ray and E.K.G.	Site of Aneurysm	Duration	Autopsy
54. Finney[13]	54	M	−	Sudden onset	Cyanosis of face, lips pale	Orthopnea	Cough	Lower extremities	No pain	Almost pulseless	Double murmur over entire sternum	—	—	Ascending aorta	24 hrs.	Communication between aorta and right branch of pulmonary artery.
55. Kraussholdt[27]	53	M	−	Sudden onset	Cyanosis	Orthopnea	—	—	Tightness in chest. Headache	Small, regular	Continuous humming murmur	Systolic	—	Ascending and arch of aorta	1 yr.	Communication between aorta and right branch of pulmonary artery through an aperture 1 cm. long. Dilatation and hypertrophy of heart.
56. Anderson[1]	33	M	−	Sudden onset	Pallor and cyanosis. Jaundice later	Dyspnea (oliguria)	Cough, hemoptysis	Lower extremities	Pain in left chest	Corrigan	Blowing double murmur	Thrill in 3rd left interspace	—	Ascending aorta. Size of walnut	4 wks.	Communication between two vessels through two apertures. Dilatation of heart.
57. Holdmoser[19]	48	M	+	Sudden onset with cough	Slight cyanosis	Dyspnea	Cough, hemoptysis	Ascites, lower extremities	Pain and pressure in chest	Fast pulse	Continuous humming murmur	Systolic with diastolic shock. 2nd left interspace	·	Ascending aorta. Size of fist	6 mo.	Communication between two vessels by wide opening with rounded edges, 1 cm. in diameter. Dilatation of entire heart.
58. Kappis[24]	44	M	−	Sudden while at work	Cyanosis	Dyspnea (oliguria)	Cough	Anasarca	Pain in precordium	Corrigan	Double murmur	Systolic thrill	—	Ascending aorta	6 mo.	Communication between aorta and pulmonary artery through aperture 6 cm. long.
59. Mallory[33]	47	M	+	Vague onset of pain in chest	Cyanosis	Dyspnea	No cough	No edema	Recurrent pain in chest	Corrigan	To and fro murmur in 3rd left interspace	Systolic thrill	Dilatation and pulsation of aortic and pulmonary conus. E.K.G.: Low ST takeoff in Leads II and IV. Elevated ST in III. Inverted T in Leads I, II, III. No axis deviation	Ascending aorta	10 days	Aneurysm ruptured into pericardium and pulmonary artery 3.5 cm. above pulmonary valves.
60. Sternberg[51]	36	M	+	Gradual onset	Cyanosis of face	Dyspnea	—	Anasarca	Pain in chest	Corrigan	—	No thrill	—	Ascending aorta	15 wks.	Communication between two vessels through 2 orifices with well rounded and smooth edges.

TABLE III—Continued

Case	Age	Sex	Syphilis	Onset	Appearance	Dyspnea	Cough	Edema	Pain in Chest	Pulse	Murmur	Thrill	Roentgen-Ray and E.K.G.	Site of Aneurysm	Duration	Autopsy
61. Correia[9]	22	M	+	Sudden onset	Cyanosis	Orthopnea	No cough	Sacrolumbar. Liver enlarged	Intense precordial pain	Corrigan	Harsh continuous murmur in 2nd left interspace	Continuous thrill in 2nd left interspace	Enlarged aorta and pulmonary conus. Total dilatation of heart. E.K.G.: No evidence of myocardial disease	Ascending aorta	2 mo. and 10 days	Communication between aorta and pulmonary artery aperture with well rounded edges 1 cm. in diameter.
62. White *[61]	74	M	+	Sudden onset in a patient with heart disease	(Negro)	Orthopnea	—	Anasarca	Substernal pain	High pulse pressure	Continuous machine-like murmur in 2nd left interspace	Continuous thrill in 2nd left interspace	Enlargement of heart, aorta, and pulmonary conus. E.K.G.: "Not remarkable"	Ascending aorta	8 mo. after clinical diagnosis	Communication between aorta and pulmonary artery, through orifice with smooth, well rounded edges 5 by 6 mm. in diameter.
63. Henry[17]		M	—	No mention of onset	—	Dyspnea	Cough, hemoptysis, previously	Anasarca	Pain in chest	No inequality of radials	Loud, rasping, prolonged systolic murmur in 2nd left interspace	Marked thrill in 2nd left interspace	—	Ascending aorta	—	Communication between aorta and pulmonary artery by way of oval aperture, long diameter ¼ inch. "Communication probably of long standing."
64. Hollis[20]	27	M	—	Sudden onset	Pallor	Dyspnea	Cough	Anasarca	Precordial pain with radiation to interscapular region	Corrigan	Continuous murmur in 2nd left interspace	Double thrill at 2nd left interspace	—	Ascending aorta	5 mo.	Two apertures communicating between aorta and pulmonary artery. One oval, 5 by 10 cm. with rounded edges; one aperture evidently of recent origin.
65. Jankovich[23] Case 1	49	F	+	+	Nothing was known of the history of the patient except that she had been in the hospital 11 months previously and was discharged. Between this and the last admission, she became progressively worse and finally entered in a moribund state. A diagnosis of aortic insufficiency was made. The statement was made that the patient probably lived a "long time following rupture."									Ascending aorta	—	Heart enlarged. Two openings from aorta into pulmonary artery, the size of a hempseed. These orifices were smooth edged.
66. Jankovich[23] Case 2	50	F	+?	Became "sick" 3 months prior to admission	—	Dyspnea (oliguria)	—	Lower extremities	—	Corrigan	Double murmur at pulmonic valve area	—	—	Ascending aorta. Size of hen's egg	3 mo.	Hypertrophy of heart. Communication between aorta and pulmonary, artery size of a "kronen," Edges of orifice smooth and rounded.

TABLE III—Continued

Case	Age	Sex	Syphilis	Onset	Appearance	Dyspnea	Cough	Edema	Pain in Chest	Pulse	Murmur	Thrill	Roentgen-Ray and E.K.G.	Site of Aneurysm	Duration	Autopsy
67. Porter [40] Case 1	55	M	+	Sudden onset following influenza	Moderate cyanosis of lips, mucous membranes, and finger tips	Orthopnea	Cough	Moderate edema of ankles	Pain in right chest	Corrigan	Harsh continuous murmur at 3rd interspace	Purring systolic and diastolic thrill	Sacular aneurysm of ascending aorta. Heart moderately enlarged and mitral shaped	Ascending and transverse aorta. Size of orange	12 days	Communication between aorta and pulmonary artery through a rough ovoid opening in aneurysmal sac 1 by 1.2 cm. in diameter.
68. Porter [40] Case 2	50	M	+	Sudden onset following exertion	No cyanosis	Orthopnea	Dry cough	Sacral, lower extremity edema. Ascites	Sense of constriction in chest	Corrigan	Whirring systolic and less distinct diastolic murmur, in 2nd and 3rd left interspaces	Purring, continuous thrill in 2nd and 3rd left interspaces	Heart enlarged. Aorta enlarged. E.K.G.: Sinus tachycardia, 115/min. Right axis deviation	Ascending aorta	6 mo.	Rounded, almost punched out, orifice 0.7 cm. in diameter connecting aorta with pulmonary artery.
69. Porter [40] Case 3	58	M	+	Sudden onset	(Negro)	Dyspnea	Dry, brassy cough	Sacral and ankle edema, ascites	No pain in chest	Corrigan	Harsh, whirring continuous murmur at 3rd left interspace	Purring continuous thrill at 3rd left interspace	Heart enlarged. Multiple aneurysms of 3 parts of aorta. Base enlarged. E.K.G.: Sinus tachycardia, 107/min. Left axis deviation	Ascending aorta and arch	2 mo.	Slit-like perforation 1 cm. in length, 2 cm. in width between aorta and pulmonary artery, situated 4.5 cm. above pulmonary valve.
70. Zabludovich [63]	46	M	+	Sudden while running	"Cyanatoid" and "erythroid"	Dyspnea	—	Anasarca	Pain in hypochondrium	Small, irregular	Intense double murmur at pulmonary area	Thrill over pulmonary valve area	Right auricle and ventricle enlarged. Aorta and pulmonary conus enlarged. E.K.G.: Auricular fibrillation. Biphasic and negative T-waves in all leads. Difference in height of ST in Leads II and III	Ascending aorta	3 yrs. (?)	Communication between aorta and pulmonary artery through an orifice with ragged edges 4 cm. long.

TABLE III—Continued

Case	Syphilis	Sex	Age	Onset	Appearance	Dyspnea	Cough	Edema	Pain in Chest	Pulse	Murmur	Thrill	Roentgen-Ray and E.K.G.	Site of Aneurysm	Duration	Autopsy
71. Walshe 58				University College Hospital, museum specimen No. 2254. "According to catalogue, 'was not detected during life by any morbid sound or symptom.' Round smooth opening ½ inch in diameter on aorta and size of split pea on the pulmonary side."												
72 to 81. *Museum Specimens*				2 specimens, Pathological Museum of Western Infirmary, Glasgow: Nos. 57, 58. 5 specimens, St. Bartholomew Museum, London: Nos. 1473, 1475, 1476, 1476A and 1477. 2 specimens, Museum of Royal College of Surgeons, London: Nos. 3164, 3165. 1 specimen, Museum of Faculty of Medicine of Paris.									All cases were of ascending aorta		
82. Case 1 (Reported in this paper)*	+	F	39	Sudden onset with exertion	(Negro)	Orthopnea	Cough and hemoptysis	Anasarca	Precordial pain radiating to left flank	Corrigan	Continuous machine-like murmur at pulmonic area	Systolic and diastolic thrill at pulmonic area	Both ventricles enlarged. Prominent aortic knob and pulmonary conus. Diodrast revealed enlargement of pulmonary artery. E.K.G.: Low T-waves in all leads. Diphasic T in Lead IVF. Sinus tachycardia 120/min. Depressed ST in Leads II and III	Arch of aorta. Size of hen's egg	5 mo.	Aneurysm of arch of aorta at junction of transverse and descending aorta. Communication with pulmonary artery through a small elliptical, smooth edged orifice.
83. Case 2 (Reported in this paper)*	+	M	40	Sudden onset while on a motor vehicle	Cyanosis of lips and mucous membranes	Orthopnea	Cough and hemoptysis	No edema	Sense of snapping in chest with pain radiating to left shoulder	Corrigan.	Continuous humming machine-like murmur at pulmonary area	Continuous thrill at pulmonic area	Enlargement of heart, aortic knob, and pulmonary conus. Large aneurysm of aorta. E.K.G.: Sinus tachycardia 122/min. No definite evidence of cardiac disease	Ascending aorta, 6 cm. by 3 cm.	6 days	Aneurysm of ascending aorta, filled with laminated clot. Communication with pulmonary through aperture 1 cm. by 2 mm. with ragged uneven edges.

aortic aneurysm was mentioned, 63 were of the ascending aorta alone (85 per cent), two were of the arch (3 per cent), six of the ascending aorta and arch (8 per cent), two of the descending aorta (3 per cent), and one of the transverse and descending aorta (1 per cent).

Usually the site may be determined by roentgenography, but frequently no evidence of such a dilatation is observed, and the aneurysmal sac is only found at necropsy.

Autopsy Findings.   In a large majority of the cases the aorta and pulmonary artery were adherent to each other through adhesions and could be separated only with difficulty.   The pulmonary artery was frequently found to be markedly dilated at its point of exit from the right ventricle, in keeping with the hypertrophy and dilation of this chamber.   This was true in the cases observed at the Charity Hospital.   These observations are in ac-

TABLE IV

An Analysis of 68 Cases of Rupture of an Aortic Aneurysm into the Pulmonary Artery Studied Clinically from the Literature, Including the Two Cases from Charity Hospital. (The number in the parentheses following each symptom or sign indicates the number of patients in which that factor was definitely discussed.)

Symptoms or Signs	No. of Cases	Per Cent of Cases
Sex (65)		
Male	59	90.8
Female	6	9.2
Onset (64)		
Sudden (with exertion)	22	34.4
Sudden (with no factor or factors unknown)	29	45.3
Sudden (miscellaneous)	9	14.1
Gradual	4	6.2
Appearance (41)		
Lividity or cyanosis	27	65.9
Pallor	6	14.6
Face pale, lips livid	5	12.2
Jaundice	2	4.9
No change (so stated)	1	2.4
Cough (42)		
Cough (alone)	20	47.6
Cough with expectoration	5	11.9
Cough with hemoptysis	14	33.3
No cough (so stated)	3	7.2
Edema (52)		
Anasarca	22	42.4
Lower extremities only	12	23.1
Lower extremities and ascites	9	17.3
Face only	1	1.9
Chest, neck, head	1	1.9
Face and extremities only	1	1.9
Sacro-lumbar	1	1.9
Lower extremities and trunk	1	1.9
No edema (so stated)	4	7.7
Dyspnea (57)		
Dyspnea (without orthopnea)	38	66.7
Orthopnea	19	33.3
Pain at Onset (45)		
Left chest or precordium (localized)	25	55.6
Chest with radiation to back, head, arms, etc.	7	15.6
Epigastric pain	3	6.7
Tightness in chest	3	6.7
Right chest	1	2.2
Hypochondriac pain	1	2.2
No pain (so stated)	5	11.1

TABLE IV—*Continued*

Symptoms or Signs	No. of Cases	Per Cent of Cases
Pulse (54)		
Corrigan (collapsing, jerking, large)	32	59.3
Abnormal (other than collapsing, as irregular, rapid, feeble)	16	29.6
Absence of	1	1.9
Not collapsing (so stated)	2	3.7
Regular	3	5.6
Murmur (56) (mainly in 2nd-3rd left interspaces)		
Continuous, humming	24	42.9
Double (systolic and diastolic)	18	33.1
Single (systolic)	13	23.2
None (so stated)	1	1.8
Thrill (44)		
Systolic	16	36.4
Continuous	9	20.5
Systolic and diastolic	3	6.8
Phase not described	11	25.0
None (so stated)	5	11.4
Roentgenography (13)		
Aortic knob enlarged	10	76.9
Aortic knob not enlarged	3	23.1
Pulmonary conus enlarged	8	100.0
(Pulmonary conus not mentioned in 5)		
Heart enlarged	10	76.9
Heart not enlarged	3	23.1
Site of Aneurysm (including autopsy and museum specimens)		
Ascending aorta	63	85.1
Arch of aorta	2	2.7
Ascending aorta and arch	6	8.1
Descending aorta	2	2.7
Arch and descending aorta	1	1.4

cord with those of Holman [21] who in considering the necropsy findings in his cases of patent ductus arteriosus found the pulmonary artery in some instances to be of even greater dimensions than those of the aorta. He also found that the right ventricle invariably was hypertrophied and dilated, concomitant with a dilated right auricle. The latter was not a rule in every case reported in the literature although one patient at Charity Hospital did present a dilated right auricle. This dilation of the pulmonary artery together with the increased size of the right heart may be explained upon the basis of the increased amount of blood in the pulmonary circuit as a result of the abnormal shunt through the arterio-arterial aneurysm. This plus the direction of flow from the aorta to the pulmonary artery as mentioned by Porter [40] determines also the proportional dilation of the artery and right ventricle and possibly the rapidity of right ventricular decompensation (*vide infra*).

Where death results suddenly following rupture, the vessel walls characteristically show a lacerated communication of variable size with ragged torn edges. Conversely, when the rupture follows a slow erosive process, the aperture presents smooth, rounded epithelialized edges, as though of a preformed orifice. The opening is usually oval.

The communication varied in type and size depending upon the nature of the rupture, whether lacerative or erosive. The average size of the orifice

ranged between 0.5 cm. and 1.0 cm. in diameter following erosion and 1.2 and 3.7 cm. in length in those which tore through. With the former, the edges of the aperture were smooth, even, rounded, whereas in the latter, the borders were rough, ragged and uneven. In several cases two or more openings were discovered.

Other tissues and organs at necropsy presented a picture of engorgement typical of that found in right and left ventricular congestive heart failure. The liver was usually enlarged and markedly engorged with blood. The lungs presented a similar picture, and there was a large amount of fluid found in the peritoneal and pleural cavities.

Disturbed Physiology

Reimann,[25] in discussing the physiologic state existing following the rupture of an aortic aneurysm into the pulmonary artery, presented an excellent description of these factors in the following words: "The effect of short circuiting the blood from an artery to a vein through an aneurysm is quite pronounced and manifested directly or indirectly upon all parts of the body. In general this depends upon the size of the communication and the amount of blood passing through. The changes occurring immediately after a fistula is opened are a fall in arterial blood pressure, increased heart rate, and increased venous pressure. The first is gradually compensated by an increase in the total blood volume, the heart rate decreases, but the action remains more vigorous and the organ hypertrophies. The systolic pressure rises to its previous height or higher, and the diastolic pressure remains low, the pulse pressure is thus increased, and the venous pressure is high. When the heart fails the signs of chronic passive congestion are manifested in all organs."

In the following discussion, an attempt is made to explain some of the outstanding signs and symptoms upon the basis of the disturbed physiology. A percentage occurrence is stated in each instance, the incidence being drawn from the review of the 68 cases sufficiently well described in the literature (tables 3 and 4).

Murmur. The majority of cases (56) in the literature presented a murmur of some nature at the second or third left interspaces. In 24 instances (43 per cent), the murmur was a continuous blowing or humming sound crescendo-decrescendo in character, frequently described as "machine-like" and resembling descriptions of the sound heard over a patent ductus arteriosus (*vide infra*). In 18 instances (32 per cent) the murmur was described as double (both systolic and diastolic) with differentiation between the two phases. White[61] states that in his case at first the sound was diagnosed as a double murmur, but that later it was realized that the murmur was continuous in character. This was true in one of the cases (case 1) from Charity Hospital. At first only a murmur in the systolic phase of the cycle was heard. Later a diastolic murmur was also heard. After prolonged

auscultation, it was finally determined that the murmur was continuous throughout the cardiac cycle and no differentiation between the phases could be made. Considering these two instances it is highly probable that many of the reports in the literature were actually of a similar circumstance.

In 13 instances (23 per cent) the murmur was described as systolic only. In one case, there was no murmur heard in the pulmonic area. In the remaining 12 of the 68 cases, either this factor was not mentioned, or the patient died before an examination could be made.

In explaining the continuous murmur heard in this condition Thurman,[55] as early as 1840, stated that as a consequence of the superior force exerted by the left ventricle, the stream of arterial blood is propelled through the aneurysmal orifice with a stronger propagation than that which the blood undergoes during the weaker and more feeble diastole. In addition the elastic reaction of the arterial system is in play during the diastolic period of the heart and thus the murmur is continued during the phase.

Another factor substantiating the expectant probability of a continuous murmur is the greater pressure in the aorta than that in the pulmonary artery. This continuous drive without the possibility of back current [5, 13, 32] produces a *veine fluide* within the pulmonary artery. The eddies are related to the sudden fall in the pressure as the blood passes from one vessel to the other. "These whirling eddies," he states, "are composed of alternating currents of blood under high and low pressure, which set the walls of the vessels as well as the edges of the opening into vibration producing thereby the characteristic thrill and bruit." The above explanation would tend to account for the sudden crescendo and slow decrescendo nature of the murmur. With the increased vigor of contraction (during systole of the heart) the murmur is heard at its loudest; with the relaxation of the ventricle the force is diminished; but although the pressure within the aorta per se drops during the diastole, it remains greater than that in the pulmonary artery, and therefore blood continues to be shunted into the latter with a diminishing velocity, thus setting up fewer and weaker eddies and consequently producing a proportional decrease in the intensity of the murmur. The sound, therefore, continues through diastole in a constant "down-hill manner." Burwell, Eppinger, and Gross [5] stated with regard to the continuous murmur that "Dynamic effects of such magnitude may be expected to produce physical signs. When a large volume of blood passes from a high pressure area to a low pressure area without going through the capillaries, as occurs in the placenta and large arterio-venous aneurysms, murmurs and thrills are produced. In these conditions, as in patients with patent ductus arteriosus, the characteristic murmur is a continuous one with systolic accentuation." The fact that a continuous murmur is not always present is attributed by Lamplough [28] to three factors: (1) disease of the aortic wall, interfering with the elasticity of the vessel, (2) presence of a large amount of blood clot in the aneurysmal sac, and (3) excessive regurgitation through the cardiac aortic orifice in diseased valves, lowering the pressure in the artery beyond.

Taylor[54] states that the murmur depends on the blood pressure about the aneurysmal orifice. An increase in the size of the pulmonary artery may lessen the pressure in this vessel, whereas narrowing of the aorta may increase it here. Taylor assumes that the pressure within an aneurysm is proportionally lower than within its vessels. This lowering of pressures might account for the double murmur heard.

In 13 instances there was only a systolic murmur. This cannot be satisfactorily explained. It might be conjectured that there is a functional opening between the aorta and pulmonary artery only during systole, influenced perhaps by a large clot in the aneurysmal sac or a peculiar type of tear. Still further Lamplough[28] in 1897 stated that a simple opening between the aorta and a venous trunk without an aneurysm probably would not produce a murmur.

Thrill. A thrill was present in 44 of the 68 patients and was described as a purring, harsh, or an intense tremor. It was systolic alone in 16 of these (36 per cent), continuous in nine (21 per cent), and systolic and diastolic in three (7 per cent). In 11 instances (25 per cent) a thrill was present but the phase of the cardiac cycle in which it occurred was not described. In five cases (11 per cent) it was stated that no thrill was observed. In the remaining 24 instances no mention was made of a thrill.

Holman[21] in his monograph on arteriovenous aneurysm has explained the thrill upon the same basis as that mentioned above in connection with the murmur, i.e., the setting into vibration of the vessel walls as well as the edges of the aneurysmal orifice by the eddies produced at the region of the rent between the aorta and the pulmonary artery.

The Immediate Fall in Blood Pressure and the Ensuing Collapsing Pulse. At the onset of the fistulous communication between the two vessels, the blood pressure, among other factors, undergoes a marked change in its character. Reimann[25] states that the systolic as well as the diastolic pressure drops to an almost imperceptible level. An adequate arterial pressure in the circulation under conditions of normality depends upon several factors: (1) the cardiac output, (2) peripheral resistance in the arteriolar and capillary beds, (3) the total capacity of the circulatory tree determined by the contraction or dilation of the vessels, (4) the total circulating blood volume,[21] and (5) viscosity of the blood. Since the alteration of any one of these factors may change the blood pressure, it is obvious that a situation such as an abnormal communication between the aorta and pulmonary artery will bring about a marked deviation of the pressure from its normal level. The abnormal fistulous aperture resulting from the rupture causes a shunt of the arterial blood and thus, by depriving the capillaries of the usual volume of circulating blood, causes a decrease in the peripheral resistance and a proportional fall in the blood pressure. As Holman[21] has stated, "obeying the law of hydraulics that flowing water seeks the line of least resistance, it is inevitable that a considerable volume of blood will be diverted from the general circulation with its high capillary resistance into the shorter circuit with

its markedly lower fistulous resistance." This condition, he continues, is similar to blood loss from excessive hemorrhage, except that here the bleeding is into the pulmonary artery.

It appears logical to assume that the degree of fall in the blood pressure depends upon two factors: (1) the size of the fistula, and (2) the amount of blood passing through the new orifice from the aortic to the pulmonary channel. Naturally, the latter is directly proportional to the former. Sudden, severe laceration resulting in a large opening will increase both factors so that the blood pressure within the arterial (aortic) stream will be markedly decreased; whereas in slow erosion with a resulting small communication a slight fall would ensue. It likewise seems logical to assume that the increased amount of blood being shunted will raise the pressure in the pulmonary system of vessels, and this plus the fact that an equal amount of venous blood will be retarded in the right ventricle, will result in decompensation and evidence of congestive failure. With a sudden shunting of blood the hemodynamics favoring a marked drop in systemic blood pressure may reach shock levels before readjustment can come into play.

To overcome this fall in blood pressure there occurs a gradual degree of compensation which may appear at once or after a short intervening period. This compensation is brought about by an increase in vigor of cardiac contractions as well as an increased cardiac rate, and by an increase in the total blood volume.[21] Due to these combined factors the systolic pressure begins to rise and reaches the level of its former height or may progress higher.[25] The diastolic pressure remains at a low level and does not rise, or if it does, only slightly and to a negligible degree in comparison to the systolic. In several experiments with artificial fistulae Holman[21] found that in every case of patent ductus arteriosus the diastolic pressure remained permanently lowered, whereas the systolic pressure was eventually restored to a normal degree.

As regards the increase in total blood volume, Holman[21] has stated that "The larger the fistula the greater will be the volume of blood flowing through the fistula. Necessarily, the compensatory changes to neutralize this loss of blood to the rest of the body must be proportional to the amount of blood so diverted, and one is justified in assuming that the increase in total volume of blood is equal to the amount of blood short circuited through the fistula."

The ensuing wide variance in the systolic and diastolic pressures after the above compensatory mechanisms have occurred, results in a high pulse pressure in the arterial stream which at the periphery produces the hydrodynamic phenomena found in aortic regurgitation such as water hammer or collapsing pulse, Duroziez's sign, increased venous pressure, capillary pulsation, and increased cardiac rate. With this also is the Hill and Rowlands sign (a large difference in blood pressure in arm and leg).[11] This latter was particularly noticeable in one of Porter's cases in which the blood pressure was 105 mm. Hg systolic and 30 mm. diastolic in the arm, over 140 mm.

systolic and 35 mm. diastolic in the leg.   In one instance at Charity Hospital (Case 2) a difference of only 122 mm. systolic and 40 mm. diastolic in the right arm and 145 mm. systolic and 60 mm. diastolic in the right leg was observed.

The pulse was described as collapsing, large, or jerking—all probably referring to the typical pulse as described by Corrigan—in 59 per cent of cases in which the pulse was reported.   There was a definite statement that no collapsing pulse was observed in two of the patients (4 per cent).   In the remaining reports, the pulse was described variously as irregular, rapid, or feeble.

Pallor and Cyanosis.   In the majority of cases reported in the literature a mention was made of the lividity or cyanosis of the patient, usually in connection with the face, lips, mucous membranes, or finger tips.   This factor was conspicuous in 27 instances (66 per cent).   A pale face with lividity of the lips was noticed in five (12 per cent).   Marked pallor was noted in six instances (15 per cent).   Jaundice of the face, sclera, and mucous membranes was mentioned as an outstanding sign in two cases.   It was stated in one instance that no change was observed.   In the remaining 27 cases no mention of the appearance of the patient was made.

The explanation of the pallor in approximately 15 per cent of cases is explained upon the shunt of blood from the aortic circulation to the pulmonic. Due to the lessened amount of circulatory arterial blood reaching the periphery, there results a marked relative anemia of the parts involved.   According to Burwell, Eppinger and Gross,[5, 12] there is a great amount of blood shunted from the aorta to the pulmonary artery in the patent ductus arteriosus. These workers in studying cases at the time of ligation of the duct of Botalli ascertained that the amount of blood short circuited through the pulmonary system amounted to between 4 to 19 liters per minute or from 45 to 75 per cent of all of the blood that leaves the left ventricle.   This blood returns to the left ventricle via the pulmonary artery and veins and thus is of no physiologic value.   "This means that the left ventricle puts out 2 to 4 times the volume expelled by the right."   Experiments by these same workers on dogs in which the subclavian artery was anastomosed to the pulmonary artery showed an increase in the amount of blood entering the pulmonary circuit to over double that observed when the circulation was intact.   Under normal conditions the rate of blood flow in the pulmonary circuit in one case quoted by Eppinger et al.[12] was 2.31 liters per minute, and after the communication was established, this increased to 5.47 liters per minute.   At the same time the peripheral flow decreased from a level of 2.31 liters per minute to 1.30 liters per minute.   These factors reveal that an extremely large amount of blood passes through the site of the rupture of the aneurysm into the pulmonary artery.   Since 45 to 75 per cent of the blood is shunted through the pulmonary circuit and thence to the left ventricle and then reshunted etc., ad infinitum, the periphery must suffer this loss until compensation can be established in one of the ways mentioned above, i.e., increased cardiac rate,

increased total volume, and increased cardiac output. Holman [21] likewise states that "when the flow is directed from aorta to pulmonary artery, a considerable volume of aerated blood is deflected from the systemic circulation, the effect of such deflection manifesting itself in a marked pallor of the skin." The net result, therefore, is pallor from an insufficient supply of aerated blood.

Since in the patent ductus, as would be the case in a communication through a ruptured aneurysm of the transverse and descending aorta, the deflection occurs distally to the subclavians and carotids, the pallor would be of the lower extremities primarily. If, however, the shunt occurred from the ascending or transverse aorta to the pulmonary artery proximal to the branching of the subclavian or carotids from the aorta, there would be a deficiency of blood reaching all parts. The site of the aneurysm in 85 per cent of cases was of the ascending aorta. The above argument would indicate that these should show a diffuse pallor. However, only 15 per cent of all reported cases had this as a prominent sign.

The explanation of the *cyanosis (66 per cent of cases)* may be upon the basis of two factors: (1) Pulmonary edema, and (2) sudden decompensation of the heart. In the former consideration one may postulate that the increased burden thrown upon the pulmonary circulation by the shunting of blood under high pressure from the aortic stream and this load added to that already emerging from the right ventricle, would so congest the pulmonary circuit that insufficient oxygenation would result. A picture of pulmonary edema simulating backward failure would appear. Eppinger, Burwell and Gross [12] state that pulmonary congestion is a constant finding in patients with patent ductus. As mentioned above, Burwell et al.[5, 12] showed clinically and experimentally that approximately 45 to 75 per cent of the blood emerging from the left ventricle was thrown into the pulmonary circulation through the patent ductus arteriosus or through experimental fistulae.

As Holman [21] states with regard to the interventricular septum defect, the "congestion has the appearance of so-called passive congestion, but it is evident that in these cases it followed not a passive but an active state of the circulation." This of course applies to the condition under discussion as well. This excessive burden added to that already present in the circuit would be more than that with which the left heart could cope at once and the edema would increase. Concomitantly the shunting blood would cause some dilatation of the pulmonary artery and quite probably some involvement of the pulmonary valves. Holman in his cases found the pulmonary artery to be dilated invariably. With this valvular involvement, a regurgitation of blood into the right ventricle results. Later right ventricular congestive failure may ensue. Holman states that in the patent ductus a dilated left heart is also characteristic. With the resulting cardiac decompensation cyanosis is the end result.

The possibility of a retrograde flow of unoxygenated blood from the pulmonary artery into the aerated aortic circulation is not to be overlooked

as a cause of the cyanosis. Unless some factor comes into play to lower the pressure within the aorta or increase that within the pulmonary artery, there is sufficient drive within the former vessel to make this hardly a factor in the production of cyanosis. Holman [21] does, however, postulate such a factor in the patent ductus arteriosus upon substantial evidence of case records and experiments. He believes that such a retrograde flow is not only possible but a fact in those instances in which there is some hypertrophy of the right ventricle. This hypertrophy, he states, so increases the pressure within the pulmonic circuit that it rises above that within the aorta. With such circumstances existing the flow of blood is then from the pulmonary artery into the aorta, thus bringing about a state of affairs, which as he suggests should be termed more accurately a "venoarterial fistula" rather than an "arteriovenous fistula." Such mixing of unoxygenated blood with the peripheral circulation could obviously cause the cyanosis observed.

Experiments by Levy and Blalock [31] and those by Eppinger et al.,[12] however, have shown conclusively that the flow of blood in the patent ductus is from the aorta to the pulmonary artery and that there is no flow from the pulmonary artery into the aorta. These investigators have found that even in the case of a fistulous connection between the two vessels in question, in which a powerful left ventricle is pumping large quantities of blood through the aperture into the pulmonary circuit, the pressure in the latter does not approach that within the aorta. As Eppinger et al.[12] state, "the obvious explanation is that the resistance in the lungs is much less than in the periphery."

Burwell et al.[12] do admit that one set of circumstances may exist that will so raise the pressure in the pulmonary artery as to exceed that in the aorta. This factor is back pressure resulting from some obstruction distal to the communication such as a failing left ventricle or some form of pulmonary disease. Above we have shown how the development of a failing left ventricle may proceed. We are not of the opinion that this is the causal agent of the cyanosis as evidenced in the patient with an aneurysm of the aorta rupturing into the pulmonary artery.

Taylor [54] has suggested that within an aneurysmal sac there is probably a decrease in pressure in relation to the parts of the vessel proximal and distal to the sac. If this be true, then there may exist some retrograde flow upon this basis. With the existence of an hypertrophied right ventricle (as suggested by Holman) in addition to the observations of Taylor, i.e., a proportional increase of pressure on one side with a proportional decrease on the other, such retrograde flow is possible and a cyanosis is explainable upon this basis. However, no work has been done along these lines to refute or substantiate this hypothesis.

Edema. In almost every instance there was edema, usually beginning in the lower extremities and gradually ascending to the scrotum, sacrolumbar region, abdomen, chest, face, and upper extremities until a marked generalized edema or anasarca resulted. In 22 cases this anasarca developed almost at

once or over a very short period of time (42 per cent). In the remaining cases in which edema was observed, it was limited to the lower extremities, face, or abdomen (table 4). As Thurman[55] stated as early as 1840, when a communication occurs between the aorta and the pulmonary artery "the whole body is the seat of dropsical effusion" as compared with the lower body edema in an arteriovenous aneurysm between the aorta and the inferior cava and an upper body edema in a case of communication between the superior vena cava and the aorta.

Recent work as described by Porter[40] indicates that the direction of the blood flow into the pulmonary artery is important in the production of such right ventricular stress. If the communication is such that the shunted stream enters in the direction of blood flow through the pulmonary artery, then we would anticipate fewer immediate symptoms of right heart failure. Pulmonary congestion with some cyanosis and dyspnea (q.v.) would be the salient feature. However, if the shunt is such that the stream hits the flowing pulmonary circuit at a right angle, there would occur a splitting of the entering stream so that almost an equal amount would go in both directions, i.e., into the pulmonary circuit away from and toward the right ventricle, thus producing an increase of load on the right ventricle. In the third possibility, the blood flow may be directly toward the right ventricle which would at once overburden the right heart and possibly result in immediate decompensation. One must keep in mind also that, as a certain additional amount of blood enters the pulmonary artery, regardless of the direction of flow, the volume in the pulmonary circuit must increase, and the pulmonary vascular bed and right side of the heart must undergo the necessary volume changes to cope with the additional volume of blood. Until the right ventricle fails, the increase in blood volume in the pulmonary circuit is taken care of by the pulmonary vascular bed.[12]

Dyspnea. Sixty-seven per cent of the patients reported had dyspnea without orthopnea. In 33 per cent orthopnea was a primary complaint. Those with dyspnea progressed rapidly to an orthopnea terminally. The explanation of this symptom is set forth by Porter.[40] He attributes the increasing breathlessness to the Hering-Breuer reflex. As he implies, the fistulous communication between the two vessels increases the amount of blood in the pulmonary circuit and thus causes an engorgement of the pulmonary vessels. Since the reflex is dependent upon changes in tension within the lung parenchyma, the added amount of inflowing blood produces the necessary stimulus, which results in dyspnea. One may also postulate that the congestion within the lungs interferes with oxygenation so that the respiratory center is stimulated. However the Hering-Breuer reflex appears to be the more important. When congestive heart failure sets in, other factors said to cause dyspnea come into play.

Cough and Expectoration. There was present a cough in 93 per cent of cases but with hemoptysis in only 33 per cent. This is explainable upon the

basis of engorgement and congestion of the lungs as well as possible pressure by the aneurysm upon the recurrent laryngeal nerve and bronchi.

Roentgenography. Roentgenographic studies were mentioned in only 13 reports, all recent. The aortic knob was enlarged in 10 patients, whereas in three no noticeable change was observed. The usual picture is that of an aneurysmal sac of varying size extending to the left of the sternum. There is usually an associated dilatation of the pulmonary conus. This latter state was present in eight of the 13 reported cases. In the other five, no mention was made of the nature of the conus. In 10 instances, the heart was enlarged, varying from "slight enlargement" to "enlargement in all directions." In most instances the heart was diffusely enlarged. This was true in the two patients seen at Charity Hospital. In these two patients fluoroscopic examination showed increased pulsations of the pulmonary vessel and pulmonary conus. Diodrast studies in one patient showed the fistula and enlarged pulmonary conus and vessels. These latter two types of roentgenographic observations proved to be of great value in the detection of the fistula.

Electrocardiography. Electrocardiographic studies were reported in six cases. They were non-specific and showed no points of similarity. In one of Porter's[40] patients, there was a right axis deviation, due probably to right ventricular strain resulting from over burdening of that chamber. There was left axis deviation in another of his patients. Mallory[33] reported a low take-off of the ST segment in Leads I and IV and an elevation of the ST segment in Lead III. There was also some inversion of T_1, T_2, and T_3. No axis deviation was noted. In one patient (Number 1) at Charity Hospital there was evidence of low T-wave in Leads I and II, and a low and notched T in Lead IVF. There was beginning right axis deviation with a depression of the ST_2 and ST_3 (possibly due to digitalis). In two of Porter's cases[40] and in one at Charity Hospital, there was evidence of sinus tachycardia. In the other patient at Charity Hospital the electrocardiogram was normal. Until further study is made with regard to the electrocardiographic changes in this condition, nothing can be stated as to definite configuration. However, from the evidence at hand, one can draw certain conclusions: (1) There may be a right axis deviation or a normal electrical axis, (2) sinus tachycardia, and (3) some change in the T-waves (lowerings, inversions, or diaphasicity) in Lead I or all three leads, with a low T-wave in Lead IVF.

The Clinical Picture

History. In 1840 Thurman[55] set down definite diagnostic criteria by which a diagnosis of a communication between an aneurysm of the aorta and the great vessels of the mediastinum could be made. His principles were:

"1.) General signs: Severe and rapidly advancing anasarca of such portions of the body as are below, or the venous system of which is distal to, the

varicose orifice. When the varicose aneurysm is between the aorta and the inferior vena cava, the legs, scrotum, and lower half of the body; when between the ascending aorta and superior vena cava the arms, face and the upper half of the body; and when between the ascending aorta and one of the right or left cavities of the heart or *pulmonary artery,* the whole body is the seat of dropsical effusion.

"2.) Livor of the face particularly, but, likewise in a less degree of all such portions of the body as are below the varicose opening.

"3.) A distended and even varicose condition of the subcutaneous veins distal to the orifice.

"4.) Dyspnea, often amounting to orthopnea, and terminating in apnea.

"5.) Cough with expectoration, especially if the sputa be bloody.

"6.) Remarkable jerking and in some cases very feeble pulse.

"7.) Emaciation, debility, loss of muscular power, deficient animal heat, and sensorial disturbances, may be looked upon as somewhat less frequent than certain signs.

"8.) Physical signs: A superficial, harsh murmur and peculiarly intense sawing or blowing sound, accompanied by an equally marked and purring tremor, heard over the varicose orifice and in the current circulation beyond it; this sound is continuous, but is loudest during systole, less loud during diastole, and still less so during the interval." [55]

In 1839 Hope [22] in his classic, "Diseases of the Heart," set forth certain signs which he considered to be pathognomonic:

"1.) A very loud, superficial, sawing murmur prolonged continuously over the first and second sounds (probably weaker during the period of repose) and loudest along the tract of the pulmonary artery.

"2.) A purring tremor in the pulmonary artery, in the interspaces between the second and third ribs.

"3.) Second sound weakened at the clavicles.

"General signs:

"1.) Jerking pulse. 2.) Great, rapid, and universal dropsy. 3). A livid venous tint. 4.) The circumstances of the symptoms having followed an effort." [22]

Pepper and Griffith [38] in 1890, commenting on varicose aneurysms of the thorax, set forth diagnostic criteria which conform closely to those mentioned by the above observers.

Clarke [7] in 1900 upon the basis of three cases added palpitation immediately following the onset of symptoms as an important complaint. He mentioned the possibility of an enlarged heart, especially the right ventricle, and also observed that the pulse, although usually of the Corrigan type, did not necessarily conform to this. In his patients there was a certain amount of euphoria. He was impressed by the oliguria present and

mentions this as an important diagnostic finding.   This has been observed in only three of the cases in the literature.

Hill and Rowlands [11] in 1922 showed that there was a difference in the blood pressure in aortic regurgitation between the arms and legs (the latter being greater than the former).   In 1923 Lewis and Drury [32] showed clinically that in arteriovenous aneurysms there was likewise present the Hill-Rowlands' sign together with other manifestations of aortic regurgitation: lowered diastolic pressure, waterhammer pulse, capillary pulsation, increased cardiac rate, etc.   (The hydrodynamic phenomenon of aortic regurgitation.)

A personal communication from William Porter [40] indicates that he recently has had three cases, two of which he has diagnosed ante mortem and upon these cases he has constructed a clinical syndrome.   This syndrome conforms essentially to the fundamentals set forth by Hope and Thurman 100 years ago.

Course.   That such a communication between the aorta and the pulmonary artery is perfectly compatible with life (for a certain length of time at least) is understandable, when one considers that the relationship only sets up an "arterio-arterial" aneurysm in which the pressure upon the arterial side is sufficient to prevent any regurgitation of the reduced hemoglobin into the aortic circuit.   Although Holman [21] believes that there is a possibility of such a retrograde flow of blood from the pulmonary artery into the aorta in the condition of patent ductus arteriosus, the recent experimental work of Levy and Blalock [31] and of Eppinger et al.[5, 12] has proved conclusively that this does not occur and that the flow is always from the aorta into the pulmonary artery.   Rupture of an aneurysm under any other circumstances results in early death.

It is true that a large number of cases did die at once or within a few hours following the rupture, but the majority of patients had a long survival.   Clerc [8] reports a case with a four year survival after evidence of rupture.   This, however, is a rare instance and some question may be placed upon the actual onset of symptoms.   The average duration of life is between six weeks and four months.

Naturally this duration depends upon the type of rupture, the size of the orifice, the amount of blood flowing through the communication and the ability of the patient to compensate.   When the rupture is sudden and the laceration great with a resulting wide fissure, the amount of blood suddenly poured into the pulmonary circuit will over burden the latter and the heart, and overwhelming symptoms and death will occur in a short period of time.   On the other hand, if a small opening is produced, though sudden, only a small amount of blood is suffused into the pulmonary stream so that life may continue for a prolonged length of time.   As Eppinger et al.[12] have stated: "Adjustment of the circulation (in a patent ductus) may be made by an increase in the output of the left ventricle.   If this is not sufficient to compensate completely for the leak there may be, in addition, a diminution in the

blood flow to the periphery." On the other hand one might assume that the increased output of the left ventricle in the case of ruptured aneurysm might only serve to increase the pulmonary congestion.

Clinical Picture. Characteristically, when the vessel walls break through, whether suddenly or through thinning and erosion, there is subjectively observed a severe pain in the left chest, with radiation to the interscapular region, head, neck, or epigastrium; a certain degree of constriction or tightness is felt within the chest, or a sense of something giving away in the precordial area. Usually this pain or constriction follows some physical exertion or frequently some illness of long duration. The characteristic picture is that of sudden onset with severe precordial pain and dyspnea following some strain as lifting a heavy load, vomiting, or paroxysms of coughing.

Rapid and progressive edema next follows, frequently beginning in the lower extremities or upper extremities and progressing until the whole body is the "seat of dropsical effusion."

When the patient is seen, the first impression is that of congestive failure with marked dyspnea, anxious facies, cyanosis, edema of limited areas or complete anasarca. There may be a state of euphoria as reported in three cases. There may be oliguria. Pallor may be present instead of cyanosis but when the former occurs it is usually limited to the upper extremities and face. The extremities are frequently cold to touch and the patient will be shaken by paroxysms of coughing with expectoration or hemoptysis. He may complain of severe degrees of palpitation.

Physical examination reveals an acutely ill patient who is exerting every effort to breathe. The lips, face and extremities are extremely pale or cyanotic. There is a progressive edema of the extremities and trunk which within a few days or hours may attain the proportions of complete anasarca. Palpation of the chest will reveal a purring or intense thrill, systolic or diastolic or both, to the left of the sternum in the second or third left interspaces in the region of the pulmonary area. Percussion will give all indications of a mass beneath or to the left of the sternum with an increase in cardiac dullness to the right. Upon auscultation a loud, humming, machine-like murmur is heard in the region left of the sternum extending from the second to the third interspaces and being continuous throughout the cardiac cycle. It is crescendo-decrescendo in character.

The hydrodynamic phenomenon of aortic regurgitation is manifest with its collapsing or Corrigan type of pulse, Duroziez's sign, capillary pulsation, increased cardiac rate, etc.

Roentgen-ray will reveal the presence of aneurysm of the aorta and in addition, marked change in the configuration of the heart boundaries. The electrocardiogram will often show some axis deviation, a sinus tachycardia, and some change in the T-wave.

Clinically, the course will continue as mentioned above along lines depending upon size of the aperture, the type of rupture, and the amount of blood passing through the orifice. The edema may subside as compensation ensues,

but eventually it will again become progressive until anasarca is predominant. Cough and expectoration will increase and hemoptysis, if not already present, will soon appear as congestion in the lungs becomes more prominent. Eventually all symptoms become more manifest until death terminates the picture in complete circulatory collapse.

THE SYNDROME

The criteria for the syndrome may be summarized as follows: From the tables as given above, and from the incidence of occurrence of the major and outstanding symptoms as presented in 81 cases recorded in the literature, and two cases observed at Charity Hospital the principal diagnostic criteria have been drawn. With these factors at hand, a syndrome has been compiled which is composed of the following essential points:

History: Sudden onset with severe stabbing pain or a sense of oppression in the precordial area with or without radiation, usually following physical exertion, and succeeded by marked and increasing dyspnea.

Subjective Signs: (1) Marked and increasing shortness of breath. (2) Progressive swelling of the lower extremities and trunk. (3) Rasping cough with expectoration or hemoptysis. (4) Bluish discoloration of the face and extremities. Pallor may be the alternative.

Objective Signs: (1) An intense thrill in the second to third left interspace occurring during systole or continuance throughout the cardiac cycle. (2) Humming "machine-like" murmur, heard best to the left of the sternum in the second or third interspaces, continuous throughout the systolic and diastolic phase and crescendo-decrescendo in character, being more intense during systole. (This murmur resembles that heard in a patent ductus Botalli.) (3) Evidence of aneurysm of the aorta. (4) Marked and increasing dyspnea usually reaching the extent of orthopnea. (5) Cyanosis of the lips, face, or extremities, or marked pallor of the same areas. (6) Edema of the lower extremities and trunk progressing to anasarca. (7) The hemodynamic phenomena of aortic regurgitation (Corrigan's pulse, increased cardiac rate, capillary pulsation, Duroziez's sign, etc.). (8) Roentgenographic evidence of aneurysmal dilatation of the aorta, prominent and enlarged pulmonary conus, and probable enlargement of the heart. (9) Electrocardiographic indications of a non-specific character but usually indicative of a sinus tachycardia, right axis deviation, and lowering, inversion, or diaphasicity of the T-waves in the standard and precordial (IVF) leads. These findings become even more significant if the patient had been studied previously and was known to have been free of the cardiovascular phenomena described above.

CASE REPORTS

Case 1. U. H., a negro female, aged 39, was readmitted to the Charity Hospital of Louisiana on July 27, 1941 and died on October 27, 1941. She had previously

been treated in 1932 for a gonococcal salpingitis at which time no symptoms referable to the thorax were noticed.

Her complaint on entry was sudden onset of pain two months before in the left chest beginning in the precordial area and radiating down into the left flank. This pain was recurring and intermittent, being precipitated by exertion, as climbing stairs, and lasting 15 minutes. The pain was described as sharp and stabbing. Soon
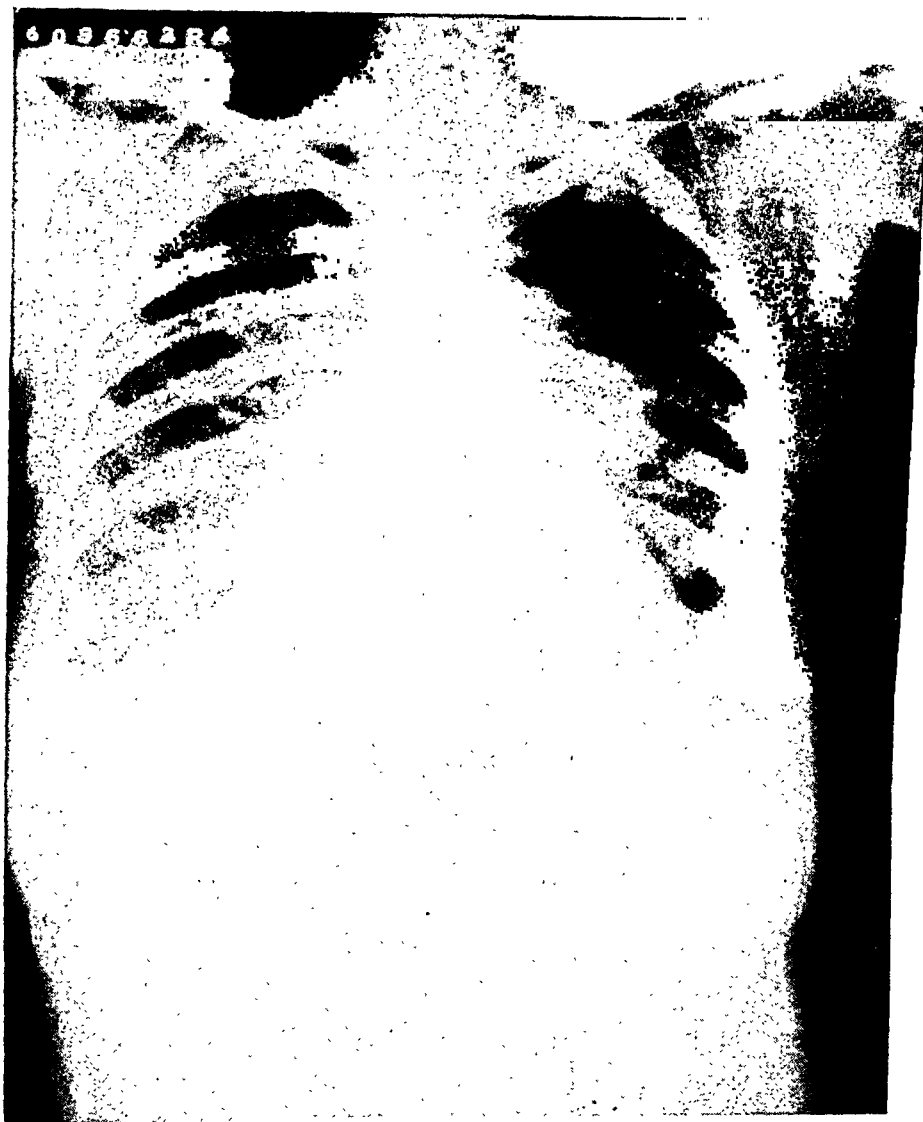
Fig. 1. Case 1. Roentgen-ray shows passive congestion of the lung fields. The heart is diffusely enlarged. Large aneurysm is present on the arch of the aorta.

after the onset of pain, the patient noticed palpitation and dyspnea which were increased by exertion, and some edema of the lower extremities. Three weeks before ascites had been observed. She had been unable to "hold anything on her stomach" since onset, and had vomited excessively. There was some weakness in the epigastrium and a precordial fullness. A "cold" and cough developed about the time of the onset and appeared to have initiated the first attack. The cough was productive of blood upon one occasion. All these symptoms had progressed since onset.

Examination upon entry revealed a well developed, negro female about 40 years of age who did not appear acutely ill but was propped up in bed in order to breathe. The examination was essentially negative except for pale conjunctivae and the findings in the chest. Over the lung fields moist inspiratory and expiratory râles were heard with some diminution of the intensity of breath sounds at posterior bases. The heart was enlarged; the apex beat was felt in the anterior axillary line in the seventh interspace. A diffuse pulsation with a marked thrill was felt over the precordial area, especially intense in the second and third left interspaces. A systolic murmur was heard at all valve areas especially loud at the pulmonic area. The pulmonic second sound was greater than the aortic second. These sounds were transmitted throughout the thorax both anteriorly and posteriorly. The murmur at the pulmonic area was described as harsh and loud. The abdomen was moderately distended but no shifting dullness was elicited. The liver was palpable on the right to a level slightly below the umbilicus. There was some tenderness in this area to deep palpation. The blood pressure was 144 mm. Hg systolic and 40 mm. diastolic and the pulse 80 per minute. The pulse was described as "pistol shot" in character.

Course in Hospital: Two days after admission, there was observed a diastolic pulmonary murmur in addition to the systolic murmur. It was described as long and low pitched. There was no enlargement of cardiac dullness. Post sacral and lower
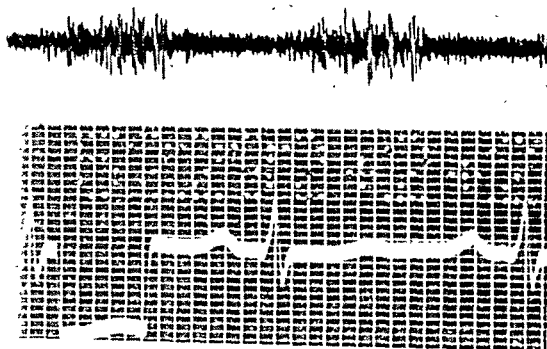
Fig. 2. Case 1. Sound tracing taken over the pulmonic valve area, showing a murmur which is continuous throughout the cardiac cycle with systolic accentuation.

extremity.edema was noted and there was some evidence of fluid in the abdomen. The Wassermann test was strongly positive. Roentgenogram of the chest revealed considerable passive congestion, enlargement of the heart, and an aneurysm of the arch of the aorta. Upon auscultation a week later, the systolic and diastolic murmurs at the pulmonic area were found to be a continuous hum in the second and third left interspaces, extending through both phases and being crescendo-decrescendo in nature. A harsh systolic and diastolic murmur was heard at apex. Fluoroscopy at that time revealed right and left ventricular enlargement with prominence of the aortic knob and pulmonary artery with marked pulsation of the left main branch of the pulmonary artery. Some compression of the pulmonary artery was postulated. Fluoroscopy indicated that an aneurysm of the left pulmonary branch might be present. On August 18, 1941 "diodrast" injections were done. These showed marked enlargement of the pulmonary artery. Venous pressure at this time was 210 mm. of water, and circulation time (arm to tongue) was 30 seconds. The patient's symptoms and edema improved under digitalis and potassium iodide therapy, but, due to gastrointestinal disturbances they were discontinued. At this time the tentative suggestion was offered that there might exist a connection between the aorta and the right heart or pulmonary artery, giving symptoms simulating a patent ductus arteriosus. For several days the patient coughed up small flecks of blood and frequently vomited.

A month after admission, the pitting edema of the ankles with some ascites was again noted, and two days later a puffiness of the face developed. Venous pressure was 280 on October 1, 1941. From that date on, the patient's condition steadily declined with increasing dropsy, dyspnea, frequent watery stools, and increased signs of failure. This progressed to termination on October 27, 1941 with signs of general cardiac failure.

The electrocardiogram showed low T-waves in all leads with a slightly diphasic T-wave in Lead IVF. The rate was 120 per minute. On August 7, 1941 a noticeable depression in the ST segments in Leads II and III was observed, which was probably due to digitalis. The T-wave in Lead IVF was low and notched. At this time, sound records were taken which showed a systolic murmur loudest at the pulmonic area with a probable soft dimuendo diastolic murmur in the same area.
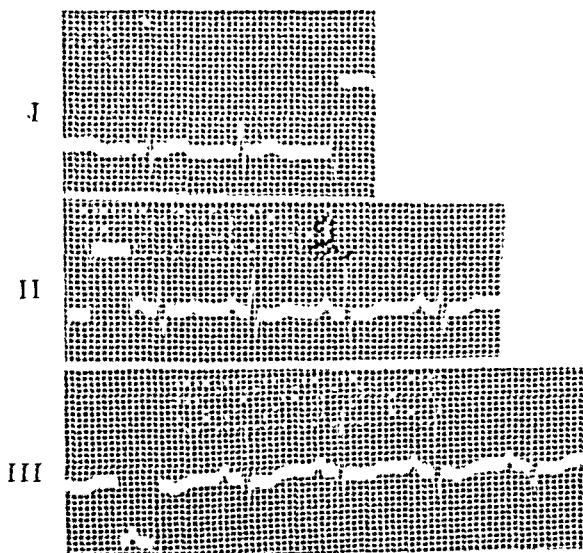
STANDARD LEADS   PRECORDIAL LEADS
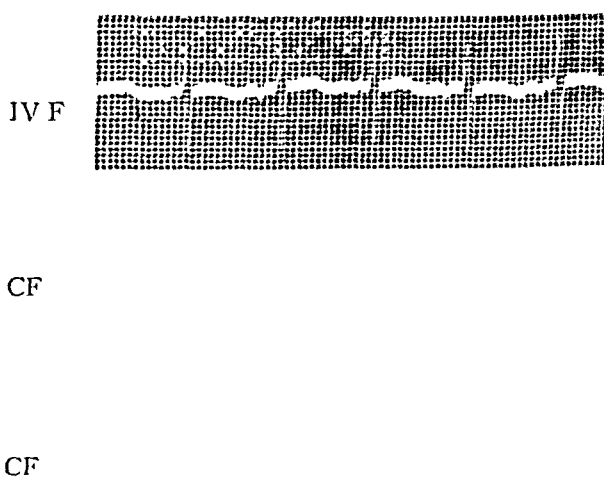
FIG. 3. Case 1. Electrocardiographic tracings show a sinus tachycardia (rate 120 per minute), a depression of the ST segments in Leads II and III (probably due to digitalis), and a low and notched T-wave in Lead IVF.

Laboratory: Red blood cells on admission were 5.4 million, and white blood cells 8000 which decreased to 5.1 million and 3000 respectively August 30. Specific gravity of the urine remained between 1.017 and 1.025 with albumin ranging from 1 to 4 plus. Many white blood cells and casts were found in the urine. The urea nitrogen varied from 21 to 44 mg. per 100 c.c. of plasma. The clinical diagnosis was communication between an aortic aneurysm and the pulmonary artery.

The findings at autopsy performed by Dr. Wm. H. Harris of the Department of Pathology at Tulane University and Charity Hospital, were as follows: A colored female weighing 115 pounds who showed marked edema of the extremities and over the sacral area. There was some jaundice of the sclerae, conjunctivae, and mucous membranes. Both pericardial and peritoneal cavities contained a large amount of fluid. The heart was enlarged, being more so in the right auricle and right ventricle. The pulmonary artery was markedly dilated at its point of origin from the right ventricle. The right and left branches of the pulmonary artery were also dilated.

A large saccular aneurysm was found on the transverse portion of the aorta in the region of the origin of the left subclavian artery. This sac was in communication with the left main branch of the pulmonary artery through an elliptical opening

measuring 6 mm. in diameter. This aperture was about 2 cm. beyond the bifurcation of the main pulmonary artery. The edges of the communication were smooth and rounded.

The detailed pathologic findings will be discussed by Dr. Schattenburg and Dr. W. H. Harris of the Department in another article.

Case 2. N. R., a colored male 40 years of age, was admitted to the Charity Hospital of Louisiana on January 2, 1942 and died January 3, 1942. His chief com-

FIG. 4. Case 2. Roentgen-ray showing marked enlargement of the heart with enlargement of the upper mediastinal shadow. A large saccular aneurysm of the aorta is present. There is some congestion of the lung fields.

plaint was chronic cough of three months' duration, and dyspnea, orthopnea, and expectoration of five days' duration. The patient stated that he had been perfectly well until three months previously when he began to have a non-productive cough which continued without any other symptoms until five days before admission when he was riding on a bus and suddenly felt a "snap" in his chest. Associated with this was an acute pain under the left shoulder and marked increasing dyspnea to orthopnea. His cough became productive and on the day of admission he noted that his sputum was blood-tinged. When he entered the hospital, he was in frank heart failure.

The review of systems was essentially negative. There was a history of a weight loss of 18 pounds in the past month, and of occasional dizzy spells with "spots before the eyes" during this same interval. His past history revealed a "double pneumonia" 18 years before and a positive syphilitic history 10 years prior to admission. The syphilis had been inadequately treated.

Physical examination at the time of admission revealed a well developed, fairly well nourished colored male who showed evidence of severe orthopnea. The blood pressure was 124 mm. Hg systolic and 40 mm. diastolic in the left arm, 122 mm. systolic and 40 mm. diastolic in the right arm and 145 mm. systolic and 60 mm. diastolic in the right leg. There was a cough which was productive of a frothy, purulent, blood tinged sputum. Slight cyanosis of the lips and mucous membranes was observed. Inspection of the chest revealed rapid respiration with a slight lag of the left hemithorax.
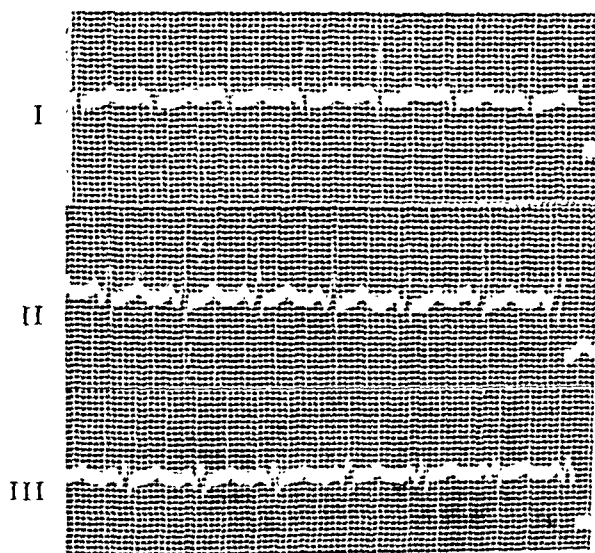
STANDARD LEADS   PRECORDIAL LEADS
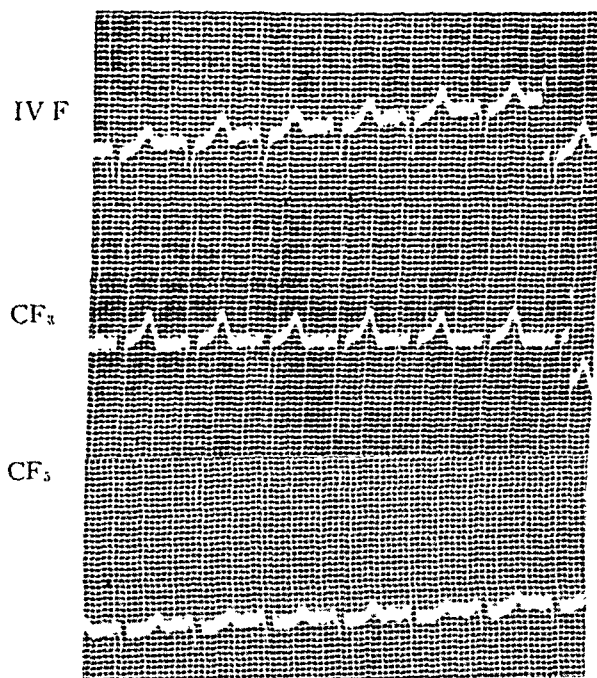
Fig. 5. Case 2. The electrocardiogram is essentially normal. There is a sinus tachycardia of 122 per minute and a slight slurring of the QRS complexes in all leads.

The apex beat could not be distinguished but a pulsating mass was observed in the suprasternal notch. There was a palpable thrill over the whole precordial area but more pronounced in the second left interspace and in the region of the pulmonary valve. This thrill could be felt throughout the cardiac cycle, being accentuated with systole. Percussion of the thorax showed a slight increase in cardiac dullness to the right and in the region of the pulmonary conus and left auricle. Auscultation revealed areas of vesicular breathing with many râles in the upper lobes, especially prominent in the right upper lobe. Inspiratory and expiratory wheezes were heard at the bases. Over the pulmonic valve area, a continuous humming machine-like murmur, not unlike that heard in a patent ductus arteriosus, was detected. This murmur was accentuated during systole of the heart. This murmur was transmitted over the whole pre-cordium and up into the neck vessels. No other murmurs were heard at the other valve areas. The radial pulse was rapid, regular, and of the Corrigan type. The remainder of the physical examination was essentially negative, except for a slightly palpable liver. *No ascites or edema of the extremities was observed.*

Course: The patient did not respond to measures instituted such as morphine, digitalis, continuous nasal oxygen, etc., but grew steadily worse. He died on January 3, 1942, twelve hours after admission to the hospital.

The electrocardiogram, taken at the time of entry, was normal. There was a sinus tachycardia of 122 per minute and a slight slurring of the QRS complexes in all leads.

Roentgen-ray showed marked enlargement of the heart, with enlargement of the upper mediastinal shadows. There was evidence of a large saccular aneurysm of the aorta. There was some congestion of the lung fields.

Laboratory Data: The circulation time was 25 seconds on the day of admission, and the venous pressure was 260 mm. of water. There was no anemia and the sedimentation rate was normal.

The clinical diagnosis was: Aortic syphilitic aneurysm with rupture into the pulmonary artery.

Autopsy Findings: The findings at autopsy performed by Dr. Philip Pizzalatto of Charity Hospital were as follows: The body was that of a colored male, weighing approximately 150 pounds. There was no edema of any part of the body. The pericardial cavity was obliterated by firm adhesions. The peritoneal and pleural cavities contained no excessive fluid. There was enlargement of the liver, the organ extending 6 cm. below the costal margin. There was marked cardiac dilatation of both sides of the heart. Approximately 3 cm. above the aortic valves on the ascending aorta there was a large saccular aneurysm, 6 cm. by 3 cm. in size. This aneurysm was filled with a laminated clot. At the inferior angle of the clot, a small aperture (1 cm. by 2 mm. in diameter) with ragged, uneven edges was found opening into the pulmonary artery just at the point of bifurcation. The aneurysm had completely obliterated the left pulmonary artery. The right pulmonary artery was quite dilated.

SUMMARY

1. The incidence of rupture of an aortic aneurysm into the pulmonary artery is unusually low when one considers the close anatomical relationship between the two vessels and the great frequency of aneurysm of the thoracic aorta. Since the first clinical instance was reported in 1812 by Wells, only 81 have been mentioned in the literature, including 11 museum specimens. This low incidence in the literature as well as the assumed infrequency of the lesion may be explained upon the basis of pin-point communications between the great vessels, oversight on the part of the pathologist when examining the aorta and the pulmonary artery, and failure to appreciate the condition clinically as a syndrome. Over a 30 year period from 1911–1941 only two instances were observed at the Charity Hospital of Louisiana at New Orleans. During this interval there were approximately 1,052,667 admissions with 1393 aneurysms of the aorta. Of these 219 were of the thoracic aorta in which 110 ruptured into various sites with only two rupturing into the pulmonary artery (1.8 per cent of all ruptures).

2. The syndrome of rupture of an aortic aneurysm into the pulmonary artery was accurately described by Hope in his "Diseases of the Heart" in 1839, his conclusions being based on one case (Munro's). His description made over 100 years ago conforms closely to the concept of the condition as understood today.

3. An analysis of the 81 cases occurring in the literature has been made in

an attempt to study the incidence of clinical manifestations which might serve as criteria for future recognition of the syndrome. The disturbed physiology which occurs in the condition of rupture of an aortic aneurysm into the pulmonary artery was also discussed. Some of the more important manifestations were:

(1) In 56 cases a *murmur* was heard in the region of the pulmonic valve. It was a continuous, humming, machine-like murmur in 43 per cent of instances, resembling that heard in a patent ductus arteriosus. It was crescendo-decrescendo in character.

(2) A *thrill* was present in 44 cases, being systolic in 36 per cent and continuous in 21 per cent.

(3) The presence of a Corrigan pulse as well as other hemodynamic phenomena of aortic insufficiency is due to the large shunt of blood from the systemic circulation into the pulmonary circuit. This deprives the peripheral circulation of a large part of its total volume.

(4) *Cyanosis* was observed (extremities, lips, mucous membranes, or total cyanosis) in 78 per cent of instances. Marked pallor was present in 15 per cent.

(5) *Edema* was found to follow cardiac decompensation.

(6) *Roentgenographic* studies were present in only 13 of the cases studied. There was observed enlargement of the aortic knob in 10; of the pulmonary conus in eight instances. The heart was enlarged in 10 of the 13 instances.

(7) The *electrocardiographic* findings recorded in six cases were nonspecific in nature. However, right axis deviation or a normal electrical axis, sinus tachycardia, and some change in the T-waves were observed in the majority of reports.

4. Upon the basis of critical analysis of the 81 cases reported in the literature and two instances occurring at the Charity Hospital, a syndrome of rupture of an aortic aneurysm into the pulmonary artery is formulated:

History: Sudden onset with severe stabbing pain or a sense of oppression in the precordial area with or without radiation, usually following physical exertion, and succeeded by marked and increasing dyspnea.

Subjective Signs:

(1) Marked and increasing shortness of breath. (2) Progressive swelling of the lower extremities and trunk. (3) Rasping cough with expectoration or hemoptysis. (4) Bluish discoloration of the face and extremities. Pallor may be the alternative.

Objective Signs:

(1) An intense thrill in the second to third left interspace occurring during systole or continuous throughout the cardiac cycle. (2) Humming

"machine-like" murmur, heard best to the left of the sternum in the second or third interspaces, continuous throughout the systolic and diastolic phase and crescendo-decrescendo in character, being more intense during systole. (This murmur resembles that heard in a patent ductus Botalli.)   (3) Evidence of aneurysm of the aorta.   (4) Marked and increasing dyspnea usually reaching the extent of orthopnea.   (5) Cyanosis of the lips, face, or extremities, or marked pallor of the same areas.   (6) Edema of the lower extremities and trunk progressing to anasarca.   (7) The hemodynamic phenomena of aortic regurgitation (Corrigan's pulse, increased cardiac rate, capillary pulsation, Duroziez's sign, etc.).   (8) Roentgenographic evidence of aneurysmal dilatation of the aorta, prominent and enlarged pulmonary conus, and probable enlargement of the heart.   (9) Electrocardiographic indications of a non-specific character but usually indicative of a sinus tachycardia, right axis deviation, and lowering, inversion, or diaphasicity of the T-waves in the standard and precordial (IVF) leads.   These findings become even more significant if the patient had been studied previously and was known to have been free of the cardiovascular phenomena described above.

5. Two cases of rupture of an aortic aneurysm into the pulmonary artery are added to the literature, one occurring in a 39 year old female who survived five months after rupture, and the other in a 40 year old male whose duration of life following rupture was six days.   Both instances were recognized and diagnosed correctly prior to death.

BIBLIOGRAPHY

1. ANDERSON, JOHN A.: Case of aneurysm of aorta perforating pulmonary artery, Glasgow Med. Jr., 1888, xxx, 283.
2. ARMSTRONG, EUGENE L., COGGINS, C. B., and HENDRICKSON, HERMAN S.: Spontaneous arteriovenous aneurysms of the thorax, Arch. Int. Med., 1939, lxiii, 298–317.
3. BENNETT, J. H.: Clinical section on principles and practice of medicine, 1859, Wood, New York, iii, 595.
4. BOYD, LINN J.: A study of four thousand reported cases of aneurysm of the thoracic aorta, Am. Jr. Med. Sci., 1924, clxviii, 654.
5. BURWELL, SIDNEY C., EPPINGER, EUGENE C., and GROSS, ROBERT E.: Signs of patent ductus arteriosus considered in relation to measurements of the circulation, Trans. Assoc. Am. Physiol., 1940, lv, 71.
6. CAYLEY, W.: Aneurysms of the ascending aorta communicating with the pulmonary artery, Trans. Path. Soc. London, 1870, xxi, 122.
7. CLARKE, J. M.: A case of varicose aneurysm of the aorta communicating with the pulmonary artery, Brit. Med. Jr., 1900, ii, 1701.
8. CLERC, P., BASCOURRET, M., and FROYEZ, R.: Communication entre l'aorte et l'arter pulmonaire par rupture d'aneurysme avec survie de plus de quatre ans, Bull. et mém. Soc. méd. d. hôp. de Paris, 1931, xlvii, 1288.
9. CORREIA, J. B.: Aneurisma da aorta roto na pulmonar, Rev. D. Assoc. Paulista de Med., 1933, ii, 321.
10. DELP, M. H., and MAXWELL, R.: Rupture of an aortic aneurysm into the pulmonary artery, Jr. Am. Med. Assoc., 1938, cx, 1647.

11. HILL, LEONARD, and ROWLANDS, R. A.: The systolic blood pressure (1) in change of posture and (2) in aortic regurgitation, Heart, 1911-1912, iii, 219.

12. EPPINGER, EUGENE C., BURWELL, SIDNEY C., and GROSS, ROBERT E.: The effects of the patent ductus arteriosus on the circulation, Jr. Clin. Invest., 1941, xx, 127.

13. FINNEY, J. M.: Aortic aneurysm communicating with the pulmonary artery, Dublin Jr. Med. Sci., 1880, lx, 170.

14. GAIRDNER, W. T.: Case of a small aneurysm of the aorta opening into pulmonary artery, Glasgow Hosp. Rep., 1889, ii, 1.

15. GAIRDNER, W. T.: Glasgow pathological and clinical society session of 1897-8. Meeting III.—13th of December, 1897: I. Specimens: Glasgow Med. Jr., 1897, xlviii, 123.

16. HANFORD, H.: Aneurysm of the aorta communicating with the pulmonary artery, Edinburgh Med. Jr., 1888, xxxiii, 695.

17. HENRY, FREDRICH P.: Aneurysm of the first portion of the arch of the aorta communicating with the pulmonary artery (spontaneous varicose aneurysm of Thurman), Univ. Med. Mag., 1888-9, i, 565. (Also in Trans. Path. Soc. Philadelphia, 1890-1), xv, 111.

18. HERAPATH, W. B.: Case of rupture of an aneurysm of the transverse part of the aorta into the pulmonary artery, Med. Assoc. Pr., 1853, p. 683.

19. HOLDMOSER, C.: Beitrag zur Symptomatologie und Diagnose der in die Pulmonalis perforirenden Aneurysmen der Aorta ascendens, Ztschr. f. klin. Med., 1907, xc, 506.

20. HOLLIS, A. U.: Aneurysm of the aorta perforating into the pulmonary artery, St. Luke's Hosp. Med. and Surg. Rep. N. Y., 1908-09, i, 168.

21. HOLMAN, EMILE: Arteriovenous aneurysm, 1917, Macmillan & Co., New York, pp. 88, 109-117.

22. HOPE, J.: Diseases of the heart and great vessels (Munro's case), 1839, Churchill, London, p. 469.

23. JANKOVICH, L.: In die Arteria pulmonalis perforierende Aorten-Aneurysmen, Wien. klin. Wchnschr., 1918, xxxi, 73.

24. KAPPIS, M.: Die Perforation eines Aortenaneurysmas in die Pulmonalarterie, Deutsch. Arch. f. klin. Med., 1907, xc, 506.

25. KAUFMAN, EDWARD: Pathology, Translated by S. P. Reimann, 1929, P. Blakiston's Sons and Co., Philadelphia, Vol. i, p. 150.

26. KORB, C., and AYMAN, D.: Aortic aneurysm rupturing into the pulmonary artery, New England Jr. Med., 1928, cxcviii, 280.

27. KRAUSSHOLDT, THEODOR: Ueber einen Fall von Aneurysma der Aorta mit Perforation in die Pulmonaire, 1893, F. Junge, Erlanger.

28. LAMPLOUGH, C.: Cases of aneurysm of the aorta communicating with the pulmonary artery, Brit. Med. Jr., 1897, ii, 392.

29. LEMANN, I. I.: Aneurysm of the thoracic aorta: its incidence, diagnosis and prognosis. A statistical study, Am. Jr. Med. Sci., 1916, clii, 210.

30. LENOBLE, M., and CHAPEL, M.: Periviscerities disséminées à forme de symphyse pericardo-perihépatique. Aneurisme sacciforme de l'aorte à son origine avec adhérence et communication avec l'artère pulmonaire sans maladie bleu, Bull. et mém. Soc. méd. d. hôp. de Paris, 1909, xxviii, 494.

31. LEVY, SANFORD E., and BLALOCK, ALFRED: Experimental observations on the effects of connecting by suture, the left main pulmonary artery to the systemic circulation, Jr. Thoracic Surg., 1939, viii, 525.

32. LEWIS, T., and DRURY, A. N.: Observations relating to arteriovenous aneurysm, Heart, 1923, x, 301.

33. MALLORY, T. B. (Editor): Case Records of the Massachusetts General Hospital: Case 27407, New England Jr. Med., 1941, ccxxv, 546.

34. McNABB, D.: Case of aneurysm of the aorta opening into the pulmonary artery, Brit. Med. Jr., 1905, i, 883.

35. Murchison, C.: Aneurysm of the ascending aorta opening into the pulmonary artery, Trans. Path. Soc. London, 1868, xix, 190.

36. Ogle, J. W.: Specimen of aneurysm of the ascending aorta communicating with the pulmonary artery, Trans. Path. Soc. London, 1852, iv, 114.

37. Peacock, T. B.: Aneurysm of the ascending aorta opening into the origin of the pulmonary artery, Trans. Path. Soc. London, 1868, xix, 111.

38. Pepper, W., and Griffith, J. P.: Varicose aneurysms of the aorta, Am. Jr. Med. Sci., 1890, c, 329.

39. Pierreson, J. H.: Aneurysme de l'aorte communicant avec l'artère pulmonaire, Bull. Soc. anat. d. Paris, 1860, xxxv, 198.

40. Porter, William B.: The syndrome of rupture of an aortic aneurysm into the pulmonary artery, Am. Heart Jr., 1942, xxiii, 468.

41. Potter, D. L.: Rupture of aortic aneurysm into pulmonary artery, Trans. Chicago Path. Soc., 1935, xiv, 240.

42. Reeves, C. E.: Observations on aneurysm of the aorta; heart diseases of Australia, 1873, J. Brooks, Australia, p. 125.

43. Reid, J.: Aneurysm of the aorta bursting into the pulmonary artery, Edinburgh Med. and Surg. Jr., 1840, liii, 99.

44. Reid, J.: Aneurysm of the aorta bursting into the pulmonary artery, Edinburgh Med. and Surg. Jr., 1840, liii, 101.

45. Reid, J.: Ibid., p. 44.

46. Roberts, W.: Case of aneurysm of the ascending aorta communicating with the pulmonary artery, Brit. Med. Jr., 1868, i, 421.

47. Rokitansky, C. F.: Krank der Anatomischen, Wien., 1852–57. Beob. Tof. 10, p. 51.

48. Scott, R. W.: Aortic aneurysm rupturing into the pulmonary artery (two cases), Jr. Am. Med. Assoc., 1924, lxxxii, 1417.

49. Smith, F. J.: Case of aneurysm of the aorta rupturing into the pulmonary artery, Lancet, 1904, i, 1119.

50. Smith, M.: Varicose aneurysm communicating with the aorta and pulmonary artery, Dublin Med. Jr., 1841, xviii, 164.

51. Sternberg, H.: Über zwei Fälle von Durchbruch der Aorta in die Arteria pulmonalis, Wien. klin. Wchnschr., 1919, xxxii, 1024.

52. Stevenson, H. N.: Aortic aneurysm rupturing into the pulmonary artery (three cases), Bull. Johns Hopkins Hosp., 1913, xxiv, 217.

53. Taylor, F.: Cases of aortic aneurysm opening into the pulmonary artery, Trans. Path. Soc. London, 1874, xxv, 56.

54. Taylor, F.: Cases of aortic aneurysm opening into the pulmonary artery, Guy's Hosp. Rep., 1883–84, xxvii, 406–425.

55. Thurman, J.: On aneurysm and especially spontaneous varicose aneurysm of the ascending aorta and sinuses of Valsalva, Med. Chir. Trans. London, 1840, xxiii, 323.

56. Turnbull, James: Cases of disease of the heart and aorta, Lancet, 1845, ii, 91.

57. Wade, W. F.: Case of aortic aneurysm in which a communication with the pulmonary was recognized during life, Med.-Chir. Trans. London, 1861, xliv, 211.

58. Walshe, Walter Hayle: The diseases of the lungs, heart and aorta, 1854, Walter and Maberly, London, 1854, 2nd ed.

59. Wells, Wm. C.: A case of aneurysm of the aorta communicating with the pulmonary artery, Trans. Soc. Improv. Med. and Chir. Knowl., 1812, iii, 85–90.

60. West, Samuel: Aneurysm of the aorta rupture into the pulmonary artery, Trans. Path. Soc. London, 1882–83, xxxiv, 64.

61. White, Paul: Rupture of aorta into the pulmonary artery with long survival, Ann. Int. Med., 1941, xv, 589.

62. Wooley, P. G.: A review of ruptured aortic aneurysms, Am. Jr. Syph., 1917, i, 426.

63. Zabludovich, S.: Sindrome de perforación del aneurisma aortico en la arteria pulmonar, Rev. d. Asoc. méd. argent., 1941, lx, 465.

TRAUMATIC HEART DISEASE: A CLINICAL STUDY OF 250 CASES OF NON-PENETRATING CHEST INJURIES AND THEIR RELATION TO CARDIAC DISABILITY *

By H. ARENBERG, M.D., *New York, N. Y.*

CARDIAC damage resulting from chest trauma has been known to occur ever since postmortem examinations became a part of medical investigation. Until recently, however, it was believed that most cases of cardiac damage were fatal, and that they occurred only in severe, penetrating chest injuries. In the past two decades, however, and particularly with the advent of electrocardiography, numerous clinical and experimental studies have demonstrated that many cases of severe cardiac damage, including rupture of the heart, result from non-penetrating chest injuries, although the thoracic cage remains intact without as much as a fractured rib.[3, 4, 5, 6, 8, 9, 13, 14, 15] Thus, out of 152 cases of ruptured heart following non-penetrating injuries to the chest gathered by Bright and Beck [7] only 58 showed evidence of fractured ribs.

These authors reported 23 authentic cases of cardiac contusion collected from the literature in which the cardiac injury did not result in immediate death. Experimentally, the same authors produced a variety of cardiac lesions in 25 dogs, five of which survived. They demonstrated numerous electrocardiographic changes not unlike those seen in man with various stages and degrees of myocardial damage. They state that most of these changes disappeared after a month or so whereas others persisted for a long time. Healing of the cardiac injury is the rule. They conclude from experimental and clinical observations that the vast majority of non-penetrating wounds of the heart are not recognized clinically and do not receive the correct diagnosis.

Erik Warburg,[16] in reviewing 225 substantiated cases of non-penetrating injuries to the heart, met with a variety of arrhythmias, including auricular flutter and fibrillation, as well as transient and permanent heart block. He describes cases of traumatic coronary occlusion and traumatic angina pectoris. He states that the best evidence of myocardial damage in traumatic chest cases is electrocardiographic changes soon or immediately after the injury.

Moritz and Atkins [12] produced myocardial contusions in 32 dogs by striking the exposed hearts with a uniform force. They noted that, pathologically, cardiac contusion is almost indistinguishable from non-traumatic myocardial infarction.

Kissane,[10] in his correlated studies of experimental cardiac injuries in 19 dogs, and of cardiac damage in 14 human beings, states that severe injury to the heart can take place in thoracic trauma without rib fracture. Electro-

cardiographically, T, ST and other changes may not appear for 24 to 48 hours after the injury had taken place and they may be transient. Other electrocardiographic changes may remain from 12 to 18 months.

Leinoff [11] presents 10 cases with electrocardiographic evidence of heart damage resulting from non-penetrating chest trauma. All survived.

Anderson [1] states that cardiac damage from non-penetrating thoracic injuries may result in death from rupture of the heart or from ventricular fibrillation. Those who survive may recover completely or may remain with symptoms of angina pectoris or of cardiac insufficiency which may eventually lead to congestive failure and death. There may, however, be immediate survival from the original chest injury, with the presence of symptoms referable only to the contusion of the chest wall; then, a latent period of several days to months follows, and the concealed cardiac injury manifests itself as an aneurysm or results in congestive failure at a later date.

Barber [2] cites symptomless cases of non-penetrating chest injuries that recovered from the original mild contusions and later died of other causes, and traumatic cardiac lesions were demonstrated post mortem.

Thus, there is no doubt that many cases of myocardial contusion or damage to the heart in non-penetrating chest trauma are missed and not diagnosed. Since physical signs of cardiac contusion or of myocardial damage are often absent if the pericardium is not involved, the condition is not recognized unless repeated electrocardiographic tracings are made. The symptoms of pain, particularly on respiration, are usually ascribed to muscular contusion, or to "traumatic pleurisy." However, more definite symptoms of an anginal syndrome or of myocardial insufficiency may develop or become apparent later, after recovery from the initial chest trauma had taken place.

In order to avoid failure in diagnosis of cardiac damage in cases of chest trauma and in order to. determine the frequency of such occurrence, it was decided to study all cases of non-penetrating chest injury admitted to this hospital. The study was made on ambulatory cases only. Every case, or as many as it was possible to investigate at a given time, admitted with a history of an injury to the chest, was carefully studied from the cardiac standpoint. In addition to a careful history and physical examination, at least one roentgenogram of the thoracic cage and a fluoroscopic examination were made. Repeated electrocardiographic tracings were made on subsequent visits in addition to the initial electrocardiogram on the first visit before a negative opinion as to cardiac damage was ventured.

Two different groups of cases were encountered and studied. One group consisted of seamen, longshoremen, Customs employees, WPA workers, and Post Office employees who sought medical aid because of an injury to the chest. The time interval between the accident and the first observation in this study varied in this group from several hours to as much as 10 weeks. The latter cases were usually those of seamen who had sustained the injury at sea, and who had not reached the home port until after a considerable length of time. Among these were individuals who had received first aid,

such as strapping of the chest aboard ship, and some who had also been ex-
amined and treated in hospitals in different countries where the ship had
stopped during the trip.   On the other hand, there were some who at first had
not considered the chest injury sufficiently disabling to merit medical atten-
tion, but reported for treatment many weeks later, when symptoms persisted
or had returned.   The period of observation during this study varied in this
group between four weeks and one year, or longer.

The second group encountered consisted of longshoremen and seamen,
and Employees' Compensation beneficiaries.   Most of these came under ob-
servation because they had complained of symptoms referable to the cardio-
vascular system which they either connected with or attributed to a previous
chest injury.   Many of these were admitted at the request of the U. S.
Employees' Compensation Commission for purposes of diagnosis and opinion
as to causal relationship between the previous trauma and the alleged subse-
quent disability.   The lapse of time between the injury in this group and the
first observation varied between three and 18 months or more.   The period
of observation in this group varied between one or two examinations for
purposes of diagnosis, to a follow-up as long as a year or more.

In the first group, the initial examination was made on 286 patients.   Of
these, 72 failed to return for reëxamination at the proper time, or did not re-
port at all; and so they were dropped from the list.   Of the remaining 214,
five were females and 209 were males.   The age extremes varied between
18 and 76 years.   In the second group, the first examination was made on 42
individuals, six of whom failed to return for follow-up or further observa-
tion.   Of the remaining 36, all were males.   The age extremes varied be-
tween 30 and 78 years.

In 168 cases of the 250 studied in both groups, chest trauma resulted
from a fall from various heights, from that of the ground level or in a bath
tub to that of two stories.   In 38 instances, thoracic trauma resulted from a
falling or swinging object striking the trunk.   In 28, injury followed crush-
ing of the chest between objects or a fall plus a blow from a falling or sliding
weight.   In 11 cases chest injury resulted from a fist fight and in eight cases
from an automobile accident.   In 84 per cent of the cases, the injuries oc-
curred on the job.   In four instances from both groups injury to the chest
occurred on two different occasions during the period of observation.

The total number of fractured ribs in both groups was 321.   There were
two fractured scapulae among these.   There was only one incident of first
rib fracture and two cases of second rib fracture.   Considering that this
study was carried out on ambulatory patients only, one would a priori con-
clude that there were no seriously injured chest cases among them.   Hence,
the chances of cardiac injury among such patients should be slight.   This
assumption might be justified for the first group of 214 cases studied.   In-
deed among this group many had rather mild impacts with resulting injury
to the chest wall and were discharged as recovered within a month or so.
The chances of cardiac injury were, therefore, comparatively small as will be

TABLE I

Non-Penetrating Chest Injuries

Age in Decades
Group I

	10–20	21–30	31–40	41–50	51–60	61–70	71–80	Totals
Number	2	16	47	68	63	17	1	214
Number with rib fractures		4	14	27	24	6		75

Group II

Number		1	6	7	11	9	2	36
Number with rib fractures			2	5	6	6	2	21
Totals	2	17	53	75	74	26	3	250

noted subsequently. The second group, however, consisted mostly of more seriously injured, many of whom had been hospitalized for a considerable period of time following the accident. Unfortunately, no serious cardiac study had been made during such period of hospitalization or soon after the accident in these cases, with the exception of three or four, and in only two instances were electrocardiographic tracings made prior to the beginning of this study. This testifies to the rarity of the occasion when an injured chest case might be considered to have also sustained a cardiac injury. It is little wonder then, that Bright and Beck [7] state that the vast majority of cases of cardiac damage in non-penetrating chest trauma are not recognized and not diagnosed.

TABLE II

Time Interval between the Accident and the First Examination in This Study

Group I—214 Cases

	3 Hours to 1 Week	1–2 Weeks	2–3 Weeks	3–4 Weeks	4–6 Weeks	6–10 Weeks	Total
Number of Cases	93	53	27	13	18	10	214

Group II—36 Cases

	3 to 6 Months	7 to 12 Months	13 to 18 + Months	
Number of Cases	16	15	5	36

Among the first group there were encountered 26 cases of various cardiac abnormalities that were thought not to be related to or influenced by the chest injury. In most cases a history of such an existing condition was obtained. Thus, there were 10 cases of hypertension, eight of arteriosclerosis, including sclerotic aortic arch and coronary disease, four of rheumatic heart disease and four of cardiovascular syphilis including two cases of aneurysm of the aorta. Most of these were more or less non-symptomatic during the period of observation for the chest injury.

Among the first group of the relatively mild, non-penetrating chest injuries, 15 cases (about 7 per cent) of cardiac damage were encountered. These were thought to be either directly due to the injury or aggravated by the injury.

CASE REPORTS

Case 1. A colored, WPA laborer, aged 50, fell from a scaffold into a manhole, about 20 feet, and struck his chest. He was treated by a local physician for about a week and when he did not improve, he came here for physiotherapy. On examination 10 days after the injury, he claimed to have been having a dull ache over the precordium ever since the accident. He never had had it before. There were no external signs of injury. Heart sounds were good in quality; rate and rhythm were normal. Blood pressure was 140 mm. Hg systolic and 90 mm. diastolic. There were fine râles in the right base; there was no evident dyspnea. Fluoroscopy of the heart and aorta was negative. Roentgenogram of the ribs was negative. Electrocardiogram was normal. Urine was normal and Wassermann reaction negative. On return for reexamination two weeks later he stated that he had not returned the week before because he had been worse and that he had been in bed since his last visit. At this time the findings were about the same except for more râles in the right base. Temperature was 37° C.

Electrocardiogram 10 days after the injury was negative except for left axis deviation and occasional extrasystole. Two weeks later T_2 was inverted and T_4 was inverted. This pattern continued on several succeeding tracings with a gradual return to normal. Fourteen weeks later T_2 and T_4 were upright. The cardiogram was considered normal.

Diagnosis. Myocardial damage following cardiac contusion, with recovery.

Case 2. A seaman, aged 42, slipped and fell on deck of the ship and struck the front of his chest. Ten days later he reached port and came to the hospital complaining of substernal and precordial pain on motion and on effort. He had never had any symptoms referable to the cardiovascular system prior to this injury.

On examination there were no external signs of injury. Heart sounds were normal, rate 90, regular sinus rhythm. Blood pressure was 106 mm. Hg systolic and 80 mm. diastolic. Temperature was 37° C. There were fine râles at the left base. Fluoroscopy showed a triangular looking heart, otherwise negative. Roentgenogram of the thorax was negative for fractures. Wassermann reaction was negative.

Electrocardiogram showed "M" type QRS_2, flat T_3, left axis deviation and shallow inversion of T_4. Four weeks later it showed improved voltage in Lead II, inverted T_3 with a well defined, upright T_4.

Diagnosis. Myocardial contusion, recovered.

Case 3. A WPA social worker, female, aged 47, was in an automobile accident and fractured her left arm and struck her chest. She was at a hospital for about 10 weeks, after which she came to this hospital for physiotherapy. She had no symptoms referable to the heart. On examination, the heart sounds were good in quality, rate and rhythm were normal. Blood pressure was 130 mm. Hg systolic and 84 mm. diastolic. Fluoroscopy of the heart and aorta was negative. Roentgenogram showed healing fractures of the fifth to eleventh ribs inclusive, on the left side in the anterior and posterior axillary line.

Electrocardiogram 11 weeks after the accident showed an isoelectric T_2 and inversion of T_3 with low amplitude of T_4. Four weeks later it showed partial inversion of T_4, in addition to T_2 and T_3 changes. Repeated examination every month showed a gradual return of the electrocardiogram to normal. Twelve months after injury T_1 was normal, T_2 still of low amplitude, but T_4 was upright.

Diagnosis. Myocardial damage, posterior lesion, recovered.
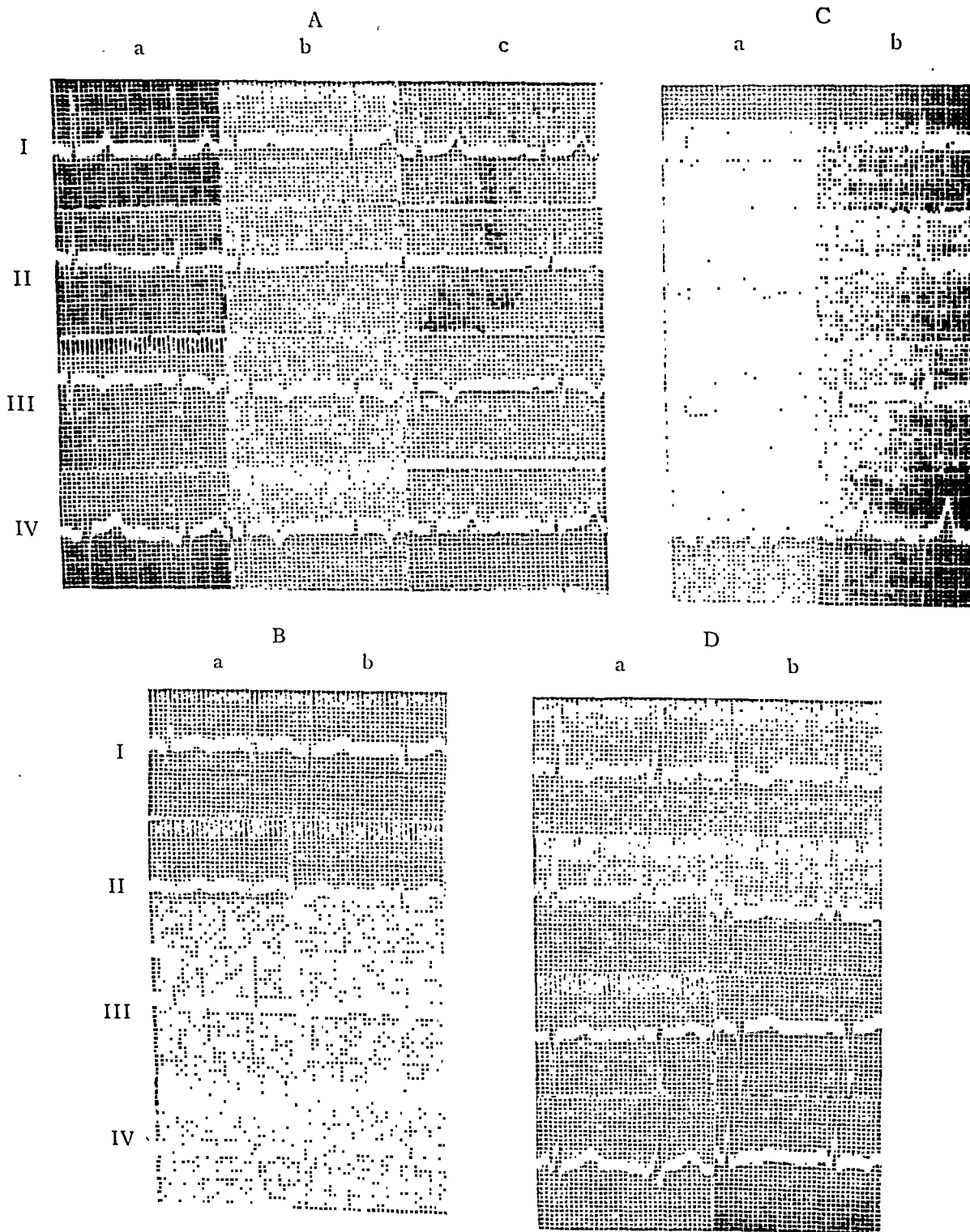
FIG. 1.

A. Case 1 (a) Taken 10 days after the injury.
(b) Two weeks later.
(c) Sixteen weeks after the accident.
B. Case 2 (a) Ten days after the accident.
(b) Four weeks later.
C. Case 4 (a) Two weeks after injury.
(b) Six weeks after injury.
D. Case 28 (a) Eleven months after the accident.
(b) Four months later.

Case 4. A Post Office employee, aged 58, fell from a height of five feet against a pile of lumber and struck his chest. He received first aid treatment and was able to resume his work. One week later he developed shortness of breath and precordial pain on effort which was thought to have been due to pleurisy resulting from the injury. On examination two weeks after the accident, the heart sounds were normal, rate 110, rhythm regular. Blood pressure was 106 mm. Hg systolic and 84 mm. diastolic. Temperature was 37° C. The bases of the lungs were clear. There was slight peripheral arteriosclerosis. Eye grounds and urine examination were negative. Fluoroscopy of the heart and aorta was negative. Roentgenogram showed fractures of the ninth to twelfth ribs inclusive, on the right side.

Electrocardiogram two weeks after injury revealed low voltage in Lead I, low amplitude of T_2; and the presence of Q_2, Q_3, and Q_4, the latter only 2 mm. deep, not characteristic. The patient was told to stay in bed for a month. Six weeks after the injury all T-waves were well defined, improved voltage in all leads, Q_2 and Q_3 much less pronounced, Q_4 absent. The patient returned six months later stating he had no symptoms and that he was able to resume his work. Electrocardiogram was negative.

Diagnosis. Myocardial contusion, recovered.

Case 5. A WPA painter, aged 58, fell off a scaffold from a height of nine feet and struck his chest against a plank. He had been in bed at home for two weeks after the injury and then came to this hospital for physiotherapy. On examination three weeks after the accident, he stated that he had never had precordial pain or dyspnea before, even on exertion, but for the past two weeks he had been having dyspnea on effort and pain over the sternum not radiating in any direction. The heart sounds were distant; rate and rhythm were normal; there were no murmurs. Blood pressure was 140 mm. Hg systolic and 90 mm. diastolic. Roentgenogram showed slight pleural effusion on the left, with fracture of the *seventh to eleventh ribs* inclusive, on the left side. The heart and aorta were normal. Temperature 37° C.

Electrocardiogram showed isoelectric T_3 and almost absent R in the precordial lead with a low amplitude T_4. Two weeks later T_1 was low and diphasic, T_2 almost flat, T_3 isoelectric, but the precordial lead was normal. Seven weeks after injury rather low T_1, otherwise normal.

Diagnosis. Probable myocardial contusion with anginal syndrome.

Case 6. A sea captain, aged 51, slipped on a gangplank and struck the left side of his chest. He had pain, but not severe enough to keep him away from his duties as Master of the ship. He reached port 10 days after the injury. On examination he complained of precordial pain radiating to the left arm. He had never had such pain before. He was well nourished and robust without evident dyspnea. Temperature was 98° F. Heart sounds were good in quality. There was a blowing systolic murmur at the apex; rate and rhythm were normal. Blood pressure was 136 mm. Hg systolic and 90 mm. diastolic. The bases were clear. Roentgenogram showed no rib fracture. Fluoroscopy showed a normal looking heart and aorta. The blood Wassermann reaction was negative.

Electrocardiogram showed partial inversion of T_4 with a Q_4 of 3–4 mm. The limb leads were normal. Ten days later, and three weeks after the injury, the T in the precordial lead was diphasic, limb leads were the same as on the first examination. Five weeks after the injury the precordial lead was normal.

Diagnosis. Contusion of the chest and myocardium, recovered.

Case 7. A longshoreman, aged 49, fell from a gangplank for a distance of 13 feet, and struck his chest. After resting for a while, he attempted to resume work, but could not on account of pain in the chest. Three days later he was taken to a hospital with pneumonia. He recovered, but continued to feel short of breath on exertion, and had precordial pain not radiating in any direction. He had never had such symptoms before the injury. On examination five weeks after the accident, he
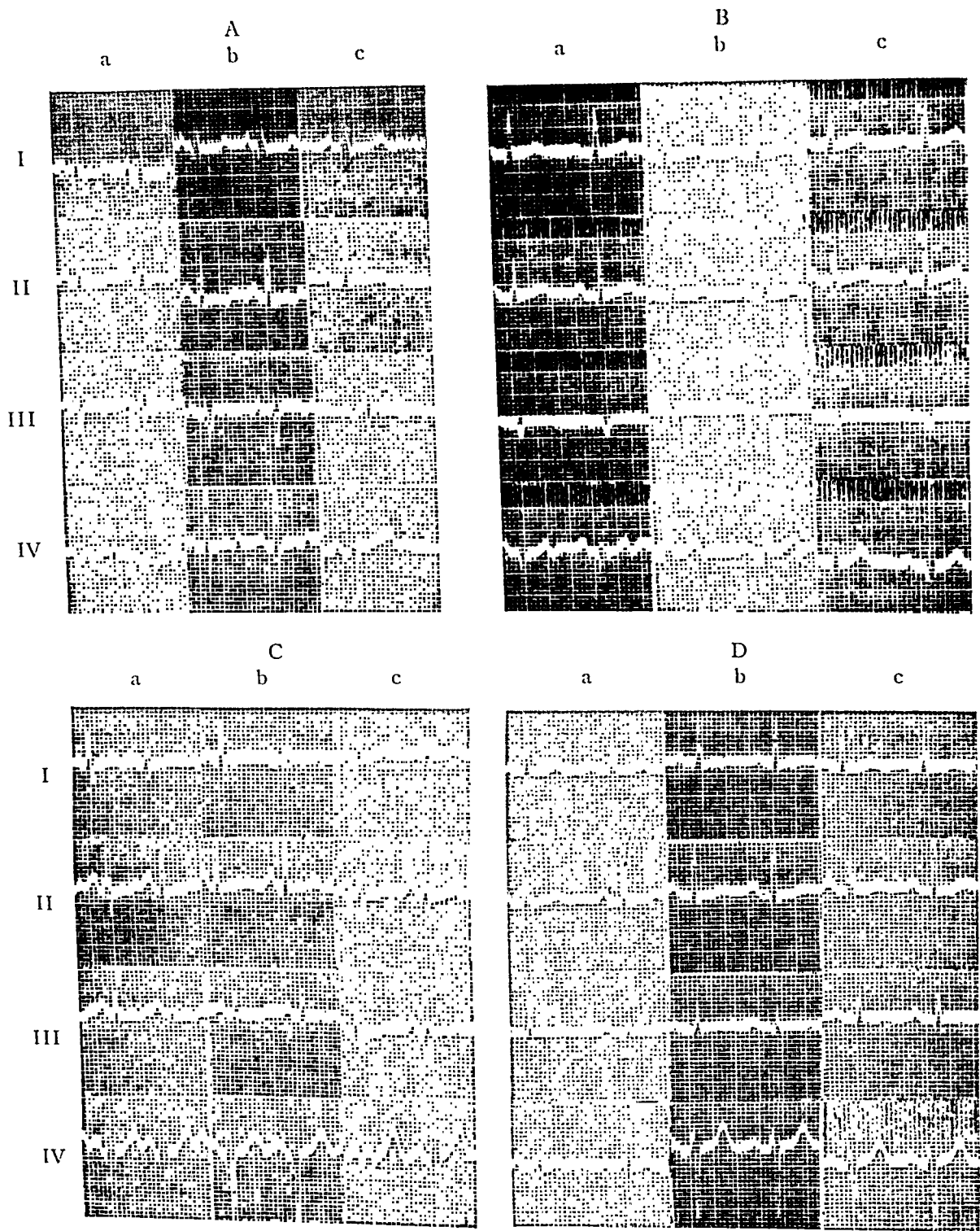
FIG. 2.

A. Case 3 (a) Eleven weeks after the injury.
          (b) Fifteen weeks later.
          (c) Twelve months after the accident.
B. Case 6 (a) Ten days after injury.
          (b) Three weeks after injury.
          (c) Five weeks later.
C. Case 7 (a) Five weeks after injury.
          (b) One week later.
          (c) Two months after injury.
D. Case 5 (a) Three weeks after injury.
          (b) Two weeks later.
          (c) Seven weeks after the accident.

appeared well nourished and had good color. The heart was not enlarged; sounds had a "tic tac" quality; rate was 110. The blood pressure was 124 mm. Hg systolic and 90 mm. diastolic. The bases of the lungs were clear. There was no edema; the liver was not enlarged. Fluoroscopy of the heart and aorta was negative. Roentgenogram showed fracture of the left seventh rib in the anterior axillary line. Electrocardiograms five weeks after the accident showed flat T_1, low T_2 and inverted T_3. One week later, T_2 was flat to partially inverted. Two weeks later, and eight weeks after the injury, the electrocardiogram returned to normal.

Diagnosis. Contusion of the chest and myocardium followed by pneumonia, with recovery.

The foregoing case reports had in common the absence of symptoms prior to the accident, the absence of physical signs such as cardiac enlargement, valvular lesions, or hypertension, which would indicate previous cardiac abnormality. In nearly all cases recovery was the rule, symptomatically as well as cardiographically. The following cases denote to a greater or lesser extent the evidence of some cardiac abnormality such as hypertension, coronary sclerosis or a rheumatic infection with cardiac enlargement, which must have antedated the injury. However, it is believed that the injury either aggravated a preexisting condition or caused superimposed damage.

Case 8. A ship's carpenter, aged 61, fell on the deck of the ship and struck his chest. He was treated by a local doctor for about six weeks and was told to return to duty. There was no record that this man had any cardiac study during this interval. On examination eight weeks after the injury, he complained of shortness of breath and pain in the chest on exertion. He had never had such symptoms before. Heart sounds were normal. There were no murmurs. The aortic second sound was accentuated. Blood pressure was 142 mm. Hg systolic and 90 mm. diastolic. There were râles and a friction rub in the left subaxillary space. Fluoroscopy revealed slight cardiac enlargement to· the left and the aortic arch was slightly widened. Roentgenogram showed fracture of the sixth to eighth ribs inclusive, on the left side. Urine was negative. Wassermann reaction was negative. Electrocardiograms eight weeks after injury revealed T_1 almost isoelectric, T_2 and T_3 inverted, T_4 bifid, slight left axis deviation. Six weeks later T_1 was well defined, T_2 low but upright, left axis deviation.

Two months later he had improved symptomatically, the pain had disappeared, but he still had shortness of breath on exertion. The electrocardiogram showed a return to normal. The blood pressure was 170 mm. Hg systolic and 102 mm. diastolic, and there was definite cardiac enlargement, indicating a preexisting hypertensive condition. Nine months after the injury he was still unable to return to his former, rather strenuous occupation, but he was able to work at light duty. The electrocardiogram showed only slight left axis deviation.

Diagnosis. Hypertension with myocardial contusion, probably related to the chest trauma.

The medicolegal aspect of this case was settled in favor of the claimant.

Case 9. A longshoreman, aged 44, was struck over the front of the chest by a steel beam of about 100 pounds in weight. On examination one day after the accident, he complained of substernal pain and "difficulty in breathing," with attacks of palpitation. He denied previous symptoms except occasional cough. The heart sounds were normal, rate 80, regular rhythm. Blood pressure was 120 mm. Hg systolic and 84 mm. diastolic. Fluoroscopy was negative. Roentgenogram revealed
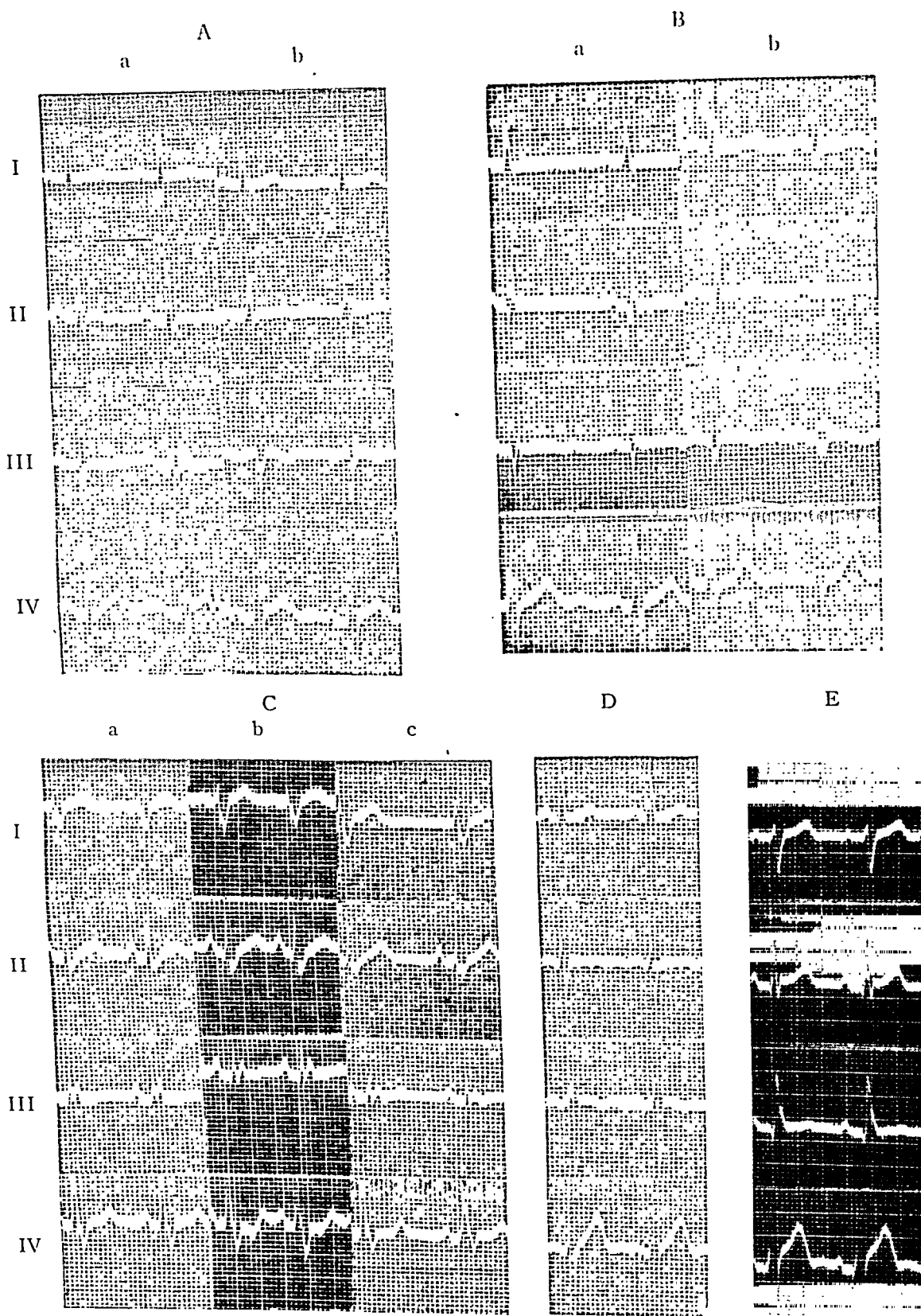
FIG. 3.

A. Case 8   (a) Eight weeks after the injury
           (b) Six weeks later
B. Case 11   (a) Seven weeks after the injury
           (b) Six weeks later
C. Case 16   (a) Four months after injury
           (b) Three weeks later
           (c) Nine months later
D. Case 19   Six months after injury
E. Case 21   Five months after injury

no fractured ribs. The electrocardiogram showed right axis deviation on repeated · examinations. He had persistent anginal attacks with occasional "rapid heart action."

Diagnosis. Anginal syndrome with possible paroxysmal tachycardia, and slight emphysema. It is believed to be causally related to the injury.

Case 10. A 54 year old seaman fell out of his bed and struck the back of his chest. On examination two days later he complained of pain below the right scapula. He also developed a cough and brought up blood-tinged sputum after the injury. The temperature was 98° F. Heart sounds were normal, rate 110, regular sinus rhythm. Blood pressure was 100 mm. Hg systolic and 70 mm. diastolic. There were râles in both bases of the lungs. Fluoroscopy showed a high left diaphragm with slight mediastinal shift to the left and increased density at the left base. Roentgenogram of the ribs was negative. Electrocardiogram two days after the injury showed marked left axis deviation, low T_1 and slurred QRS complexes. He continued· to get anginal attacks for several months but he gradually improved. The electrocardiogram showed no change.

Diagnosis. Coronary sclerosis, old, with anginal syndrome which was probably aggravated by the chest trauma.

Case 11. A Post Office laborer, 62 years of age, was struck over the left side of the chest by a sliding, heavy, wooden box. He was able to continue to work, but three days later he began to have precordial pain on exertion. There was a history of hypertension without symptoms. On examination six days after the injury took place, he was tender over the left axillary region. There was a long, blowing systolic murmur over the apex, no thrill, rhythm was normal, rate 76. Blood pressure was 156 mm. Hg systolic and 88 mm. diastolic. Bases of the lungs were free. There was no edema of the extremities. There was slight peripheral arteriosclerosis, and slight changes in caliber of the retinal arteries. Fluoroscopy showed moderate to marked cardiac enlargement to the left and right, with prominence of the aortic arch. Roentgenogram was negative for fractures of the ribs. The urine showed a faint trace of albumin. Electrocardiogram seven days after the injury showed isoelectric T_1, almost flat T_2 and T_3, with Q_2 and Q_3. Six weeks later T_1 became upright and T_3 inverted. All QRS complexes were slightly slurred.

Diagnosis. Hypertensive heart disease with myocardial damage, the latter probably precipitated or aggravated by the chest trauma.

Case 12. A longshoreman, aged 54, was thrown against the side of a ship when he was struck by a swinging draft of castor beans of almost 500 pounds weight. He was taken to the hospital by ambulance, had his chest roentgen-rayed, and was· sent home. He was treated by a local physician for about six weeks. No study was made of his heart. On examination 10 weeks after the accident he denied ever having had cardiac symptoms before. He stated that two days after the injury he had developed shortness of breath, palpitation and pain in the chest. He spat up bloody sputum for several days. He had not ·been able to return to work because of dyspnea on effort. The heart was enlarged to the left. Sounds were distant, rhythm irregular, rate 100. There was a blowing systolic murmur at the apex and a distant, late, diastolic murmur at the same area. Blood pressure was 118 mm. Hg systolic and 84 mm. diastolic. There were no râles in the lungs. There was no edema; the liver was not tender. Eye grounds were not remarkable. Fluoroscopy showed marked enlargement of the heart to the right and left with obliteration of the retrocardiac space by an enlarged left auricle. Roentgenogram of the ribs was negative. Wassermann reaction and urine were negative. Electrocardiogram showed auricular fibrillation, rate 100, with no axis deviation.

Diagnosis. Probably rheumatic heart disease with failure precipitated by trauma.

In this case the possibility of a ruptured mitral valve or damaged *papillary* muscle could be considered as a diagnosis. However, the marked cardiac
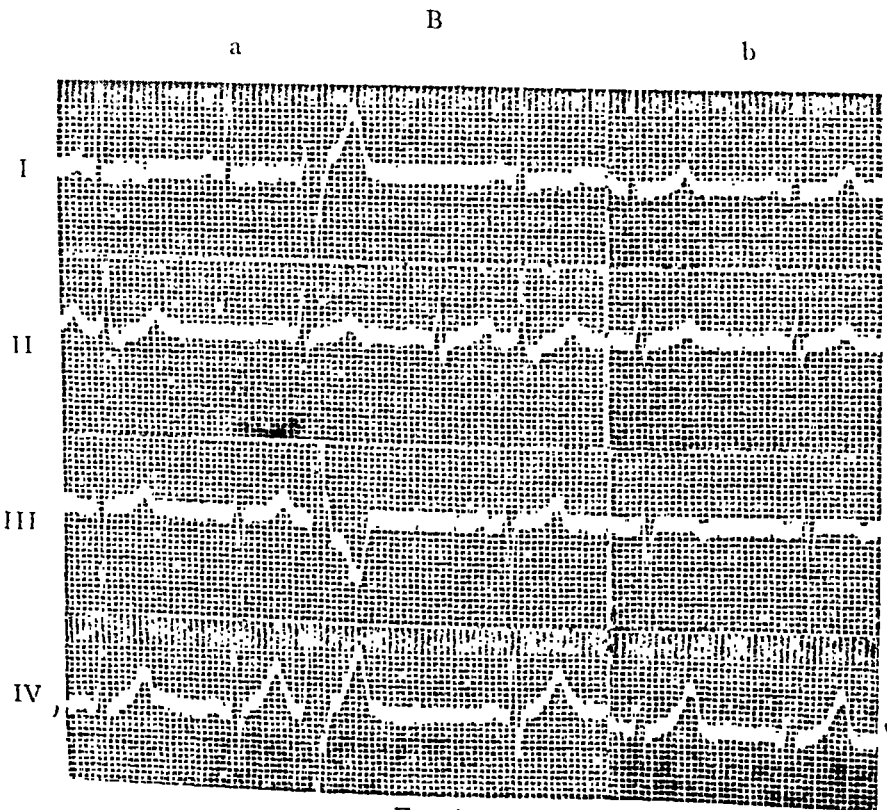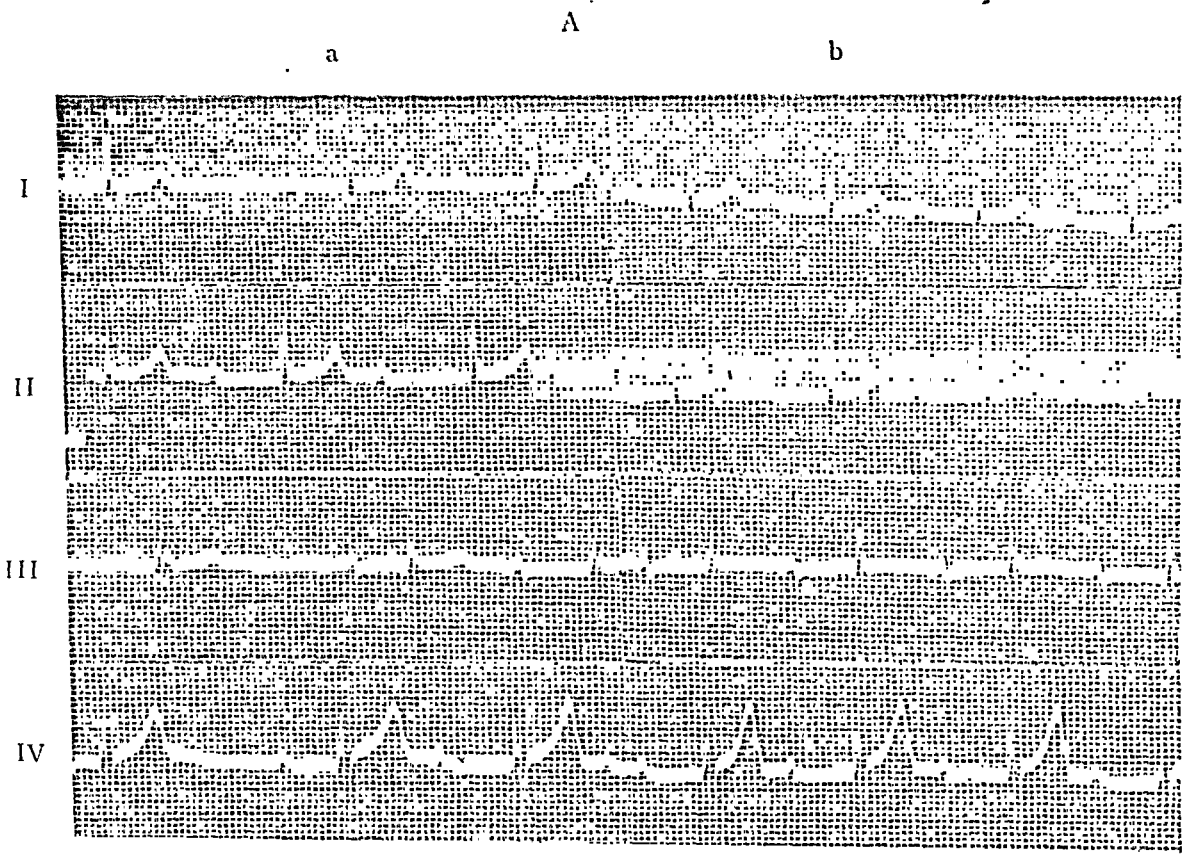
Fig. 4.

A. Case 17 (a) Twenty months after the accident
(b) Two weeks later
B. Case 18 (a) Six months after the injury
(b) Three months later

enlargement noted 10 weeks after the accident was more easily explained by a probable previous rheumatic endocarditis, even though the history was of no help in this respect. Medicolegally, the disposition of this case was in favor of the claimant.

Case 13. A longshoreman, 31 years of age, fell from a height of 10 feet and struck his chest against a cement floor. He did not lose time from work, but noticed "palpitation and fluttering" since the accident. On examination six weeks after the injury, the heart was not enlarged, sounds were normal, rate 74, with frequent premature beats. Blood pressure was 108 mm. Hg systolic and 80 mm. diastolic. Fluoroscopy was negative. Roentgenogram of the thorax was negative for fractures. The electrocardiogram showed numerous ventricular extrasystoles. The latter continued subjectively for about two months and subsided.

Diagnosis. Extrasystolic arrhythmia, probably precipitated by chest trauma.

Since no time from work was lost in this case, compensation was not awarded.

Case 14. A customs guard, 50 years of age, slipped from a staircase and fell against a rail, striking the front of his chest. One week later he began to have pain in the chest which did not radiate in any direction. The pain was not accompanied by dyspnea; it was worse on exertion, and was relieved by rest. On examination three weeks after the injury, the findings were entirely negative. Blood pressure was 118 mm. Hg systolic and 84 mm. diastolic. Fluoroscopy was negative; and roentgenogram of the thorax revealed no fractures.

Electrocardiogram showed low QRS_2 of the "W" type with a deep Q_3, 9 mm., and S_1. The cardiogram did not change on subsequent examinations whereas the symptoms varied from time to time.

Diagnosis. Coronary disease, old, with anginal syndrome, possibly aggravated by the injury.

Case 15. A longshoreman of 50 fell from a height of about 10 feet and struck his chest, elbow and leg. He attempted to continue to work, but was forced to give up on account of pains. He was examined six days after the injury by the carrier's physician and was sent to the hospital where he had remained for 11 days, after which he had been given out-patient treatment for about six weeks. No cardiac study was made at that hospital.

On examination about 10 weeks after the accident he stated that he had been short of breath on slight exertion, accompanied by precordial pain. He had never had such pain before, and never had been short of breath.

He was obese and was somewhat dyspneic during the examination. Color was fair. Heart sounds were normal, rate 100, regular rhythm. Blood pressure was 160 mm. Hg systolic and 116 mm. diastolic. There was no edema and there were no râles in the bases. There were no remarkable changes in the eye grounds. Fluoroscopy showed slight left ventricular enlargement, but roentgenogram of the heart was negative. The left side showed healing fractures of the seventh to ninth ribs inclusive at the anterior axillary line. Urine revealed a slight trace of albumin. Electrocardiogram showed slurring of all QRS complexes, with deep Q_3 and inversion of T_3 on three different occasions.

Diagnosis. Coronary disease with anginal syndrome, the latter probably precipitated by the thoracic injury.

The U. S. Employees' Compensation Commission allowed partial claim in this case.

In addition to the above cases there were two others in which, subsequent to the injury, paroxysmal tachycardia appeared on occasions although it was said never to have existed before. Because no electrocardiographic record was ever made of the tachycardia attack, the case records are not reported and not included in the list.

Among the 36 individuals studied in the second group, there were two cases of chronic nephritis, two of cardiovascular syphilis and three of hypertension, who were not considered disabled. These conditions were not influenced by the injury in question. Thirteen out of 36 were found to have been suffering from conditions which were thought to be either caused or aggravated by the accident.

Among these cases there was a more definite and persistent attempt on the part of the patient to ascribe all the symptoms to the injury. Whereas in the previous group, in most instances the individual complaining of symptoms referred to the chest, in this group many of them definitely pointed to the heart and were "heart conscious." In many instances this attitude was the result of attempts at medicolegal action or of measures preparatory to such claims because of the accident.

CASE REPORTS OF GROUP II

Case 16. A seaman, aged 46, fell off a ladder and struck his chest, then dropped 10 feet lower and struck his left side against a rail. He received first aid treatment aboard ship and roentgenographic examinations and treatment at several ports in Europe and Asia during his trip. He was told "two ribs were broken on the left side near the heart." He worked only part of the way. He came to this hospital four months after the accident when he reached home port. On examination he complained of shortness of breath on exertion accompanied by pain around the heart. This began about two months following the accident. He had never had such symptoms before. There was, however, a questionable history of pulmonary tuberculosis. The heart was not enlarged; sounds were good in quality; rate and rhythm were normal. Blood pressure was 100 mm. Hg systolic and 84 mm. diastolic. Fluoroscopy was negative. Roentgenogram showed no fractures of the ribs, but revealed evidence of healed apical tuberculosis. The blood Wassermann reaction was negative. Urine was negative.

Electrocardiogram four months after the accident showed intraventricular block. Three weeks later there was no change except for a depression in the ST_4 segment. Nine months later there was still evidence of intraventricular block, but with the precordial lead nearing the normal.

Diagnosis. Intraventricular block, permanent, probably resulting from myocardial contusion.

Case 17. A machinist of 42 was violently blown out of a boiler which he had been repairing aboard a ship, by a sudden blast of compressed air and steam. He was thrown for a distance of 12 feet against an iron grating and he received a severe blow on the left side of the chest. He was hospitalized for several months. At the hospital it was discovered within about a month after admission that he had "heart block." He was treated as an out-patient for another year or so.

On examination a little over 18 months after the accident, he claimed that he had been suffering from shortness of breath on exertion and that he had not been able to return to work because of that. He had no rheumatic or syphilitic history. He stated that prior to the accident he had never lost a day from work because of illness.

His work was rather strenuous. There were no external abnormalities. Heart sounds were of good quality at times and muffled at other times. The rate was 44 and the rhythm irregular. Blood pressure was 110 mm. Hg systolic and 90 mm. diastolic. Fluoroscopy revealed a normal looking heart and aorta with slow and irregular action. Roentgenogram of the thorax was negative for fractures. Blood Wassermann reaction and urine were negative.

Electrocardiogram 20 months after injury showed auriculo-ventricular block, with an auricular rate of 56 and a ventricular rate of 46. Both were irregular. There were no other changes. There was no change after exercise. Two weeks later rhythm was regular, the auricular rate 66 and the ventricular rate 66. The PR interval was .44 second. After exercise, it returned to the identical rate with dissociation as in the previous tracing.

Diagnosis. Complete heart block, permanent, following chest trauma.

The medicolegal aspect was decided in favor of the claimant and full compensation was granted by the U. S. Employees' Compensation Commission.

Case 18. A longshoreman, 61 years of age, fell down into the hold of a ship for about 16 feet. He was unconscious and was taken to a hospital where he remained for 11 days. Subsequently he was treated with physiotherapy for about five months, as an out-patient, by the carrier's physician. The hospital record revealed "the presence of auricular fibrillation with partial heart block, rate 42, due to old coronary disease." No electrocardiogram nor roentgenogram of the heart was made. On examination ·six months after the accident he complained of shortness of breath and of occasional precordial pain. He stated that he had never had such symptoms before, and that he had never lost time on account of heart ailments, even though he had been doing strenuous work. He showed no dyspnea during examination. The heart sounds were distant. There were no murmurs. There was a trigeminal rhythm. Blood pressure was 140 mm. Hg systolic and 92 mm. diastolic. There were no râles in the bases; and there was no edema. There was moderate peripheral arteriosclerosis and slight narrowing of the retinal arteries. Urine showed a faint trace of albumin, no casts. The Wassermann reaction was negative. Fluoroscopy showed no cardiac enlargement and the aorta was normal. Roentgenogram showed a healed fracture of the fifth rib on the right side at the midclavicular line.

The electrocardiogram showed a ventricular, premature contraction every third beat with inversion of T_1 after every normal beat, and left axis deviation with slurring of all QRS complexes. There was no history of digitalis medication. Three months later the trigeminal rhythm disappeared, and T_1 became upright. There was left axis deviation and slight slurring of QRS complexes.

Diagnosis. Myocardial damage with anginal syndrome following chest trauma; old coronary disease.

Partial compensation was granted by court.

Case 19. A seaman, aged 42, fell down in the engine room from a height of about five feet to the floor. He struck his elbow and chest. He was hospitalized on account of an infection that developed at the site of the injury of the elbow. During his stay at the hospital he had no cardiac symptoms and no study of the heart was made. On examination six months after the injury, he stated that he had been having precordial pain and a "jumpy feeling in his heart" for about three months; that is, it began about three months after the accident. He had never had such symptoms before. There were no external signs of injury. Color was good. No dyspnea was noted. Heart sounds were good in quality; rate and rhythm were normal; blood pressure was 110 mm. Hg systolic and 80 mm. diastolic. Fluoroscopy was negative.

Roentgenogram showed fractured left fifth and sixth ribs in two places, healed. Blood Wassermann reaction was negative. Electrocardiogram showed slurred QRS, marked left axis deviation, partial inversion of T_2 of low amplitude, and inversion of T_3.

Diagnosis. Anginal syndrome with coronary disease, probably precipitated or aggravated by the chest injury.

Case 20. A longshoreman, 37 years of age, fell from a height of 10 feet and struck his chest. He was taken to the hospital, and there he developed "pneumococcal pleurisy." He was discharged three weeks later and was treated for several months by a local physician for his fractured ribs. There was no record of any cardiac study. On examination five months after the accident, he stated that he had been having pain in the left side of the chest on effort, ever since the injury or soon after that; rest relieved the condition. He had never had such symptoms before. The past history was not significant. Findings were entirely negative, aside from a blood pressure of 80 mm. Hg systolic and 64 mm. diastolic. There was dyspnea at rest. Fluoroscopy was negative. Blood Wassermann reaction and urine were negative. Roentgenogram showed healed fractures of the fifth to the ninth ribs, inclusive, on the left side.

Electrocardiogram showed slight slurring of all QRS complexes with slightly widened S_1 and S_2, but with the QRS interval within normal limits.

Diagnosis. Coronary disease with angina pectoris; the anginal syndrome was probably initiated by the chest trauma.

Compensation was granted in this case until symptoms subsided.

Case 21. A seaman, aged 40, jumped out of a second story window while intoxicated. He was hospitalized for three months and was discharged as recovered. The hospital diagnosis was "multiple fractures of the first to seventh ribs, inclusive, on the right side; of the mandible and of the greater trochanter on the right side." Roentgenogram reported a "mitral configuration of the heart, but there was no enlargement. Clinically, the heart was negative." No electrocardiogram was made. On examination here, five months after the accident, he complained of precordial pain of two weeks' duration, with dyspnea on exertion. He denied syphilitic or rheumatic infection. The heart was enlarged to the right and left. There was a questionable gallop rhythm at the apex, rate 110. No murmurs were heard. There was no palpable thrill. Blood pressure was 110 mm. Hg systolic and 80 mm. diastolic. Bases were clear. There was no edema nor tender liver. Temperature was 37° C. Urine was negative. Wassermann reaction was negative. Fluoroscopy showed symmetrical enlargement of the heart on both sides, with a straight left border. Roentgenogram showed healed fractures of the upper seven ribs on the right side.

Electrocardiogram showed right axis deviation, slight ST_2 and ST_4 elevation, with slurring of QRS complexes.

The patient did not return for another examination until nine months later. At that time, the electrocardiogram had not changed and the symptoms occurred less frequently. The physical signs did not change.

Diagnosis. Myocardial damage following injury, probably superimposed upon a previous, quiescent, rheumatic heart disease.

The following cases demonstrate by the history, by the evidence of cardiac enlargement, as well as by the blood pressure, that preëxisting cardiac disease was present, but that the previously existing condition was not disabling, and did not prevent the individual from following up his occupation prior to the accident; that is, the preëxisting condition was quiescent or asymptomatic, but a break occurred or was initiated as a result of the injury or coincidental with the injury.

Case 22. A colored winchman, 63 years of age, fell on the deck and struck his chest when he was hit by the flap of a heavy canvas tent, against which a gust of wind suddenly blew. He received first aid and continued to work for several days. He had to give up work, however, as he began to feel short of breath. He was treated by a local physician for two months and when he became worse, he was hospitalized.

On examination seven months after the injury, he complained of shortness of breath and pain in the chest not relieved by rest, but aggravated on effort. He had two periods of hospitalization, one of 11 days, the other of 20 days. The hospital diagnosis was hypertensive and arteriosclerotic heart disease with decompensation. He claims never to have lost time because of sickness before. He used to have attacks of hiccups, and following the accident these had become worse and more frequent, so that an attack of singultus might last several weeks. It was in such a state that he had been admitted to the hospital on the second occasion.

At the time of examination at this hospital he appeared dyspneic. The heart was enlarged to the left; sounds were normal. There was a distant systolic murmur at the apex, rate 80, rhythm regular. The lungs were clear. There was slight edema of the ankles. The blood pressure was 200 mm. Hg systolic and 104 mm. diastolic. There was moderate peripheral arteriosclerosis and tortuosity of the retinal vessels. Urine showed a trace of albumin, but was otherwise negative. Wassermann reaction was negative. Fluoroscopy revealed slight dilatation of the ascending portion of the aorta and marked enlargement of the left ventricle. Roentgenogram showed no fractures of the ribs. He had had no digitalis for several weeks. Electrocardiogram showed high voltage, horizontal RT_1 and RT_4 depression, with marked axis deviation.

Diagnosis. Hypertensive and arteriosclerotic heart disease with mild congestive failure, probably precipitated by the chest trauma.

Partial compensation was awarded by the U. S. Employees' Compensation Commission.

Case 23. A longshoreman, aged 46, fell about 15 feet from a ladder to the boiler room. He fractured his right femur and hurt his chest. He had to undergo an operation for osteomyelitis of the femur as a result of the injury from which he apparently improved. Two years later, however, his heart became "bad," and he was told at a hospital that his heart condition had resulted from the injury of the chest.

On examination about 24 months after the injury, he appeared to be in a moderate degree of congestive heart failure. He showed pallor, dyspnea, orthopnea, râles in the bases, and peripheral edema. The heart was enlarged to the left; sounds were distant; rhythm was regular; and there were no murmurs. Blood pressure was 160 mm. Hg systolic and 128 mm. diastolic. He had had no digitalis. Urine showed a trace of albumin and a few hyaline casts. Fluoroscopy revealed moderate concentric hypertrophy of the heart in all directions. The aorta was full. Roentgenogram showed healed fractures of the right second rib and of the right scapula.

Electrocardiogram showed inversion of T_1 and T_2, diphasic T_4, and notching and slurring of QRS complexes, with an interval of .11 second.

Diagnosis. Hypertensive heart disease with myocardial damage and congestive heart failure, possibly related to a previous myocardial contusion.

Medicolegally this case was still pending and partial compensation was allowed.

Case 24. A longshoreman, 53 years of age, fell to the lower hold of the ship, about 28 feet, and broke "the cartilagenous sixth to eighth ribs" on the left side. Several hours after the accident, he developed dyspnea, orthopnea and cyanosis, with

auricular fibrillation. He was hospitalized and treated subsequently for about a year. On examination one year after the injury, he stated that he had been short of breath on the least exertion and had been taking digitalis ever since the accident. Before the injury he never was ill and was a hard worker, climbing four to five flights of stairs in his work, without symptoms. He had no rheumatic fever history and no syphilis. The heart was enlarged to the left; sounds were of good quality. There was a systolic murmur at the apex; rate was 110, irregular. Blood pressure varied between 160 mm. Hg systolic and 90 mm. diastolic and 200 mm. systolic and 104 mm. diastolic. The bases were clear. The liver was not tender. There was no edema. Color was good. There was no evident dyspnea at rest. Wassermann reaction was negative. Urine showed 4 plus albumin and hyaline and finely granular casts. The eyegrounds revealed changes in caliber of the arteries, no hemorrhages. Fluoroscopy showed moderate enlargement of the left ventricle. The aorta was normal. Roentgenogram of the chest showed no fractures.

Electrocardiogram revealed auricular fibrillation with digitalis T-waves, and right axis deviation. Several repeated cardiograms showed no changes.

Diagnosis. Hypertensive heart disease with auricular fibrillation and questionable old rheumatic mitral disease. Congestive failure was probably precipitated by the thoracic trauma.

This case was decided in favor of the claimant.

Case 25. A WPA architect, aged 64, fell on a level ground, struck his chest and fractured his left shoulder and humerus. He was never able to return to work because of shortness of breath which began after the accident. Recently the dyspnea had become much worse. He had had occasional "smothering sensation in the chest" for 10 months before the injury. On examination 11 months after the accident, he appeared obese and was slightly dyspneic. Heart sounds were good in quality; rate and rhythm normal. There was a fairly loud systolic murmur at the apex and base. Blood pressure was 150 mm. Hg systolic and 90 mm. diastolic; 170 mm. Hg systolic and 94 mm. diastolic. There were scattered râles in both bases. There was no edema. Fluoroscopy showed marked enlargement and triangular appearance of the heart, with prominence of the aortic arch. There were no rib fractures. Urine was negative.

Electrocardiogram showed a normal sinus rhythm, left axis deviation and T_1 inversion. There was moderate slurring of all QRS complexes and a low T_2. Four weeks later the T in the precordial lead became partially inverted and of low amplitude. No digitalis.

Diagnosis. Hypertensive heart disease with coronary disease, and myocardial damage probably aggravated by the injury.

Case 26. A longshoreman, aged 60, was struck over the chest by a bag of coffee weighing about 100 pounds. After resting for a while, he resumed work. The next day he was not able to work because of pain in the front and back of the chest. Two weeks later he developed shortness of breath which had become progressively worse. Since then he had not been able to return to work. He had never lost time from sickness before.

On examination about six months after the injury, he did not appear in distress, and his color was good. Heart sounds were masked by a long, blowing systolic murmur that was heard all over the chest. There was no thrill. Rhythm was regular, rate 100. There were no râles in the lungs and no edema. Blood pressure was 170 mm. Hg systolic and 96 mm. diastolic. He had had no digitalis. Urine was negative. Roentgenogram was negative for rib fractures. Fluoroscopy showed moderate enlargement of the left ventricle. The aortic arch appeared normal.

Electrocardiogram showed rather high voltage, slurring of all QRS complexes, and marked left axis deviation.

Diagnosis. Hypertension with coronary disease and anginal syndrome, probably initiated by the chest injury. The possibility of an injury to the mitral valve or papillary muscle was considered.

The following case reports illustrate more or less of a quiescent period or of only mild symptoms following the injury to the chest, terminating in one case in acute coronary occlusion and subsequent anginal attacks, and in the other in progressive anginal attacks and diminished cardiac reserve.

Case 27. A WPA carpenter fell off a scaffold, dropped about 15 feet, and struck his chest. He was treated for several weeks and was able to return to work. He continued to have occasional dull pain in his chest and shortness of breath on climbing stairs. One day, while at work, five months after the accident, he was seized with severe precordial pain and was taken to the hospital. The hospital record gave the diagnosis as "acute anterior myocardial infarction following a coronary occlusion." He recovered, but has not been able to return to work on account of frequent attacks of pain. He was examined here on three different occasions from eight to 12 months following the accident and three to five months following the coronary occlusion episode. The findings on all occasions were entirely negative, objectively. Blood pressure was 144 mm. Hg systolic and 90 mm. diastolic. Fluoroscopy was negative, and roentgenogram showed no evidence of fractured ribs. Wassermann reaction was negative. The electrocardiogram revealed slightly low voltage in all leads on all tracings.

Diagnosis. Myocardial contusion followed by coronary thrombosis and later by an anginal syndrome.

Case 28. A longshoreman, aged 59, fell off a hatch cover and struck his chest against a mooring winch. He was given first aid, had his chest strapped, and was allowed to continue his work. Several days later he began to feel pain and shortness of breath, so that he was not able to continue his work. He began to feel worse as time went on until he was having symptoms even at rest. On examination four months after the accident, he denied ever having had such symptoms before. He had had no rheumatic fever or syphilis. He appeared robust, and not in distress. There was slight carotid throbbing, but no distention of the veins in the neck. Heart sounds were distant and irregular, rate 104. No murmurs were heard. Blood pressure was. 110 mm. Hg systolic and 90 mm. diastolic. There were no râles in the lungs, no edema, nor tender liver. The thyroid was negative. Slight changes in caliber in the retinal arteries were present. Roentgenogram showed healed fractures of the ninth and tenth ribs on the right side. The left ventricle was enlarged two plus, with no auricular enlargement.

Electrocardiogram showed auricular fibrillation, rate 100, no shift in the electrical axis.

Diagnosis. Auricular fibrillation with angina pectoris, probably followed chest trauma.

Temporary compensation was allowed by the U. S. Employees' Compensation Commission.

Discussion

As it appears from the case reports, nearly all the cases of cardiac damage in both groups were at the age when coronary disease and hypertension are most prevalent. Of the 28 cases, only three were in the early fourth decade. Table 1 shows that 60 per cent of all the individuals studied were in the fifth

and sixth decades of their lives, and 75 per cent of all the positive cases were in the same age group. This disproportion is presumably due to the fact that a large number of individuals in this age group was not entirely symptomless prior to the injury. It is well known, however, that a previously diseased heart is more vulnerable to trauma than a normal heart, and that greater damage is likely to result from injury to a heart or myocardium previously diseased, than from trauma to a normal heart under similar circumstances.

It is notable that the severity of the chest trauma and the chances of cardiac damage do not necessarily correspond. There were many cases of severe chest injury with bilateral rib fracture of as many as 11 and 13 ribs without cardiac involvement. In one instance an individual 56 years of age with a huge syphilitic aneurysm of the arch of the aorta sustained a moderately severe chest injury with fractured ribs, when his ship was torpedoed and he was exposed in a lifeboat for 48 hours. He showed no cardiac damage and was able to return to duty in less than three months. On the other hand, several cases of severe cardiac contusion with resulting permanent conduction defect were met with in individuals in whom no rib fracture or injury to the sternum was discovered. It is apparently the degree of elasticity of the chest wall and the type of blow which determine the chances of cardiac injury by anteroposterior compression. It is also conceivable that in cases in which fracture of ribs does occur, the force of the impact or blow is broken or diminished, thereby causing less or no damage to the substratum. In general, the greater the elasticity of the chest wall, the more chance for injury to the structures beneath, provided the impact is the same. In the cases reported here, the greater degree of cardiac damage occurred mostly among those who had sustained no rib fracture. In cases in which cardiac injury was considered to have taken place and in which fractured ribs were found, the latter occurred in a proportion of four on the right side to six on the left side of the chest.

The outstanding thing noted is that so few cases with relatively severe chest trauma had had a complete cardiac examination in instances in which the individuals were under treatment by the carrier's physicians. Nearly all those received physiotherapy for a relatively long time. Apparently it is still believed that the chest wall is a sufficiently strong barrier to internal injury in non-penetrating wounds, and that cardiac damage is the greatest rarity in such instances. Very possibly, many cases of cardiac disability allegedly resulting from trauma would have been eliminated from this number if a careful cardiac examination including a roentgenogram and an electrocardiogram had been made immediately after the accident. Since recovery is the rule in these cases, it is conceivable that if the cardiac injury had been discovered and the individuals treated accordingly, many cases might not have gone into the chronic stage or even have died eventually from the direct or indirect effects of the injury. It would also obviate and simplify many medicolegal problems, perhaps to the mutual advantage of plaintiff and defendant.

It is admitted, however, that in many instances it is very difficult to decide whether or not the cardiac disability is related to the trauma. It is to be borne in mind that many patients are apt to attribute any and all ills to a previous injury, particularly when symptoms emanate from, or near, the site of the injury. The tendency for some injured to exaggerate symptoms for purposes of compensation should not be overlooked. The writer had to testify in many of the above cases as an impartial examiner either at the request of the Government or either side, and he can appreciate the difficulties involved.

BIBLIOGRAPHY

1. ANDERSON, R. C.: Non-penetrating chest injuries, Brit. Med. Jr., 1940, ii, 307.
2. BARBER, HUGH: Contusion of myocardium, Brit. Med. Jr., 1940, ii, 520.
3. BECK, CLAUDE S.: Contusion of the heart, Jr. Am. Med. Assoc., 1935, civ, 104–109.
4. BILDERBECK, A. C. L.: Traumatic rupture of the heart without fracture or external lesions, Brit. Med. Jr., 1919, i, 675.
5. BISHOP, L. F., JR.: Trauma and its relation to heart disease, New York State Jr. Med., 1940, xl, 1099.
6. BOAS, ERNST P.: a. Angina pectoris and cardiac infarction from trauma or unusual effort, Jr. Am. Med. Assoc., 1939, cxii, 1887. b. Some immediate causes of cardiac infarction, Am. Heart Jr., 1942, xxiii, 1.
7. BRIGHT, E. F., and BECK, C. S.: Non-penetrating wounds of the heart, Am. Heart Jr., 1935, x, 293.
8. BURSTEIN, J., and MARSHAK, R. H.: Contusion of the heart, New York State Jr. Med., 1940, xl, 59.
9. HAMILTON, J. H.: Traumatic rupture of the heart without external injuries, Brit. Med. Jr., 1934, ii, 1101.
10. KISSANE, R. N.: Cardiac contusion, Practitioners Lib. of Med. and Surg. N. Y., 1941. ANN. INT. MED., 1937, ii, 907.
11. LEINOFF, H. D.: Direct non-penetrating injuries to the heart, ANN. INT. MED., 1940, xiv, 653.
12. MORITZ, ALLAN R., and ATKINS, JOSEPH P.: Cardiac contusion, Arch. Path., 1938, xxv, 462.
13. RAFASINGHAM, A. S.: Massive hemopericardium with recovery after paracentesis, Brit. Heart Jr., 1939, i, 181.
14. SCHLOMKA, C.: Experimentelle Untersuchungen über den Einfluss stumpfer Brustkorbtraumen auf das Herz, Ztschr. f. d. ges. exper. Med., 1934, xciii, 751.
15. SPICER, FRANK S.: Trauma and internal disease, 1939, J. P. Lippincott Co., Philadelphia, 182.
16. WARBURG, ERIK: Traumatic heart disease, 1938, Oxford University Press, New York City. Myocardial and pericardial lesions due to non-penetrating injury, Brit. Heart Jr., 1940, ii, 271.

CASE REPORTS

MYCOTIC ANEURYSM: REPORT OF A CASE[*]

By J. P. EICHHORN, M.D., and CURTIS F. GARVIN, M.D., *Cleveland, Ohio*

VIRCHOW[1] in 1847 described arterial dilatation developing at the site of embolism, and subsequently the rôle of embolism in the production of certain aneurysms came to be generally recognized. The term "mycotic" was adopted to call attention to the etiologic importance of infection. The term is somewhat misleading since a special group of infections has come to be called the mycoses, but it is sanctioned by long and general use.

Mycotic aneurysms are comparatively rare. Any artery may be involved, the aorta most frequently. Mycotic aneurysms usually occur in association with endocarditis lenta. The pathogenesis of the condition may be by (1) the lodgment of infected emboli or bacteria in the lumina of vessels or in the vasa vasorum, or (2) the extension of infection from the aortic or pulmonic valves.

Mycotic aneurysms vary greatly in their appearance, size and other characteristics. As a rule the original embolus cannot be identified. The affected artery shows various degrees of inflammation, destruction, and dilatation with thrombus formation and perhaps healing. Rupture often occurs, leading to free bleeding or the formation of false aneurysms consisting of hematomata which communicate with the lumen of the vessel and which are surrounded by adventitial or perivascular tissue.

The clinical diagnosis of mycotic aneurysms is made only exceptionally. It usually depends on the occurrence of embolism followed by the development of a pulsating tumor.

A patient with a mycotic aneurysm has recently been observed at the Cleveland City Hospital. The case is of interest in that the diagnosis could be made clinically. The process involved the common iliac artery, one not commonly affected.

CASE REPORT

O. M., a negro, 34 years of age, who entered Cleveland City Hospital August 5, 1940, complained of pain in the right side of the chest. He had had rheumatic fever in 1919 and had been observed periodically since 1934 in the dispensary because of rheumatic heart disease. During the month previous to admission he had fever, sweating at night, malaise, weakness, pain in the chest, and had lost 15 pounds in weight.

Examination showed that the patient was normally developed but poorly nourished and acutely ill. The temperature was 38.5° C., and the pulse rate was 126 per minute. The eye-grounds and conjunctivae were normal. The heart was enlarged, and there was a loud systolic murmur at the apex. The cardiac mechanism was normal and

the blood pressure was 136 mm. Hg systolic and 74 mm. diastolic. The lungs were normal. The edge of the liver was 1 cm. below the costal margin. No other organs or masses were palpable in the abdomen. There were no signs of myocardial insufficiency.

Roentgenologic examination of the chest showed the left ventricle and pulmonary conus to be enlarged. The erythrocytes numbered 3,500,000 per cu. mm. and the hemoglobin was 9.0 gm. per 100 c.c. of blood. The white blood cell count was 20,000 per cu. mm. The urine contained white blood cells, grade 2, and red blood cells, grade 1. The urea nitrogen was 5.8 mg. per 100 c.c. of blood. Electrocardiograms taken in August and October were normal. Seventeen blood cultures were negative; one taken October 14 revealed the presence of *Streptococcus viridans*.

The condition of the patient became progressively worse. The temperature varied from 37.0° C. to 40.4° C., and chills occurred frequently. On September 4 he complained of pain in the left ankle, and the pulsation of the dorsalis pedis artery on that side was found to be decreased. Petechial hemorrhages in the conjunctivae were present from time to time.

On September 30 he complained of abdominal pain. Examination revealed a tender, pulsating mass approximately 5 cm. in diameter in the lower umbilical region. October 9 the face was edematous and a pericardial friction rub was heard. The urea nitrogen on October 15 was 88.6 mg. per 100 c.c. of blood. The patient died October 15. The clinical diagnosis was rheumatic heart disease, endocarditis lenta due to *Streptococcus viridans*, mycotic aneurysm of the aorta, focal glomerulonephritis, uremia, and uremic pericarditis.

Autopsy Findings. (Autopsy performed by Dr. Vladimir M. Sasko.) The body was that of a poorly nourished colored man.

The pericardial sac contained 200 c.c. of yellow-green, clear fluid having a specific gravity of 1.015. The heart weighed 495 gm. The epicardium was normal. There was a recent infarct involving most of the left ventricle and the septum. The mitral leaflets were thickened and firm, and nodular vegetations, varying in diameter from 1 to 20 mm., were attached to the margin of each. The chordae tendineae were thickened and shortened. The other valves showed no endocarditis. Numerous mural thrombi were found in the left ventricle and the right atrium.

The coronary arteries showed very slight sclerosis. In the descending ramus of the left coronary artery, 4 cm. from the ostium, there was an embolus which resembled the vegetations in appearance.

The aorta was normal. The left common iliac artery and the left hypogastric artery were dilated, forming a red-brown, firm, oval-shaped mass measuring 3 by 4 by 5 cm. Upon section, this mass consisted of red-brown, laminated thrombus with a white center. The lumina of the vessels were not occluded.

The lungs showed several septic infarcts and bronchopneumonia. The spleen weighed 95 gm. and was the seat of recent and old infarcts. The kidneys together weighed 470 gm. and contained many infarcts.

Microscopic examination of a section of the occluded coronary artery revealed suppurative arteritis around a thrombus which contained hyaline material similar to that found in the vegetation on the mitral valve. The lesion in the myocardium had all the features of a septic infarct. Sections of the left common iliac and the left hypogastric artery showed the arterial wall and the contained thrombus to be the seat of severe suppurative inflammation. Numerous cocci in chains were present in the sections of the vegetation, the embolus in the coronary artery, the myocardial infarct, and the aneurysm of the common iliac artery. The kidneys showed acute and subacute focal glomerulonephritis. *S. viridans* was recovered from the heart's blood and the vegetations on the mitral valve.

The anatomical diagnosis was chronic rheumatic heart disease, endocarditis lenta

of mitral valve (*Streptococcus viridans*), embolism of the left coronary artery with occlusion of the descending ramus, septic infarct of the left ventricle and septum, and mycotic aneurysm of the common iliac and left hypogastric arteries.

COMMENT

The development of a pulsating abdominal tumor in a patient suffering from endocarditis lenta could scarcely be mistaken for any other condition. The associated pain, the rather sudden appearance of the mass, and the occurrence of embolism elsewhere were helpful in arriving at the clinical diagnosis.

SUMMARY

The appearance of a painful, pulsating abdominal mass in a patient suffering from endocarditis lenta led to the clinical diagnosis of a mycotic aneurysm. Autopsy showed the aneurysm to involve the left common iliac and the left hypogastric artery. The patient also had coronary embolism, with resultant myocardial infarction.

BIBLIOGRAPHY

1. VIRCHOW, VON RUD.: Ueber die akute Entzündung der Arterien, Virchow's Arch. f. path. Anat., 1847, i, 272–378.

CARDIAC ANEURYSM: REPORT OF A CASE WITH CORRELATION OF CLINICAL, RADIOLOGICAL AND ELECTROCARDIOGRAPHIC FINDINGS *

By DRIVER ROWLAND, M.D., *Hot Springs, Arkansas*

UNTIL recently cardiac aneurysm, though common at autopsy, has not often been diagnosed clinically.[1] Up to 1930 only 10 cases had been diagnosed premortem.[2] Today, although the diagnosis is by no means commonplace, it is made more and more frequently.

The clinical,[1] radiological,[3] and electrocardiographic [4] features of cardiac aneurysm have been described, but the possibility of diagnosing this condition is not appreciated by most internists and cardiologists.

Because of this condition it was thought desirable to report a case diagnosed clinically as a cardiac aneurysm, and attempt to correlate the clinical, radiological, and electrocardiographic features of value.

CASE REPORT

The patient came under observation December 12, 1940, because of shortness of breath. For years the patient had had indigestion every spring which lasted a few weeks and then disappeared. About three months previously he had had an attack of indigestion similar to those he had had in the past. These attacks of indigestion were characterized by epigastric pains about two hours after meals, relieved by food. Soon

after this indigestion began the patient had a very severe attack of pain accompanied by quite a bit of nausea and vomiting, beginning in his epigastrium and radiating to his substernal region and down his left arm. This severe pain lasted six to eight hours and required morphine for relief. Two days later the patient had a similar attack which lasted for only 30 minutes to an hour and was much less severe.† He had had no pain since. Soon after these attacks of pain the patient noticed he had marked shortness of breath, both at rest and on exertion. This was so marked and he became so easily exhausted that it became necessary for him to remain in bed for two months. During this time he had severe palpitation and noted that his heart beat very rapidly. At the time he came under observation he was up several hours a day, and was somewhat better. He still became short of breath on moderate exertion, but there was no orthopnea. The patient's past history was irrelevant. His father and mother were both living, and, although elderly, were in excellent health. The patient smoked in moderation, did not use alcohol, drank one cup of coffee daily.

Physical examination revealed an average white male, 42 years of age, apparently not acutely ill. His blood pressure was 120 mm. Hg systolic and 100 mm.
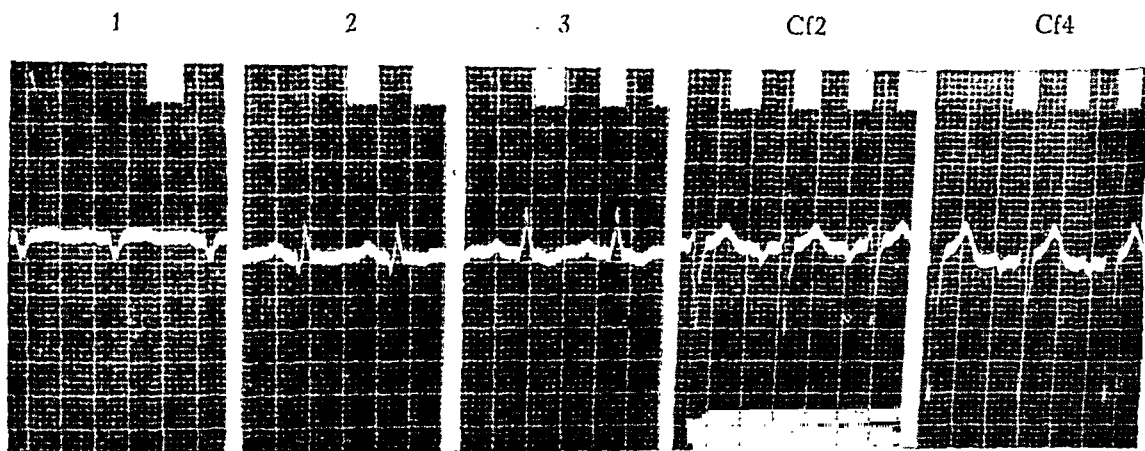
FIG. 1. Electrocardiogram showing right axis deviation.

diastolic, pulse 110, respiration 16. The examination was negative except for the cardiovascular system. There were a few fine râles present at the right lung base. Examination of the heart disclosed the point of maximum intensity to be in the sixth left interspace about 5 cm. outside the midclavicular line. The cardiac impulse extended from mesial to the midclavicular line to the anterior axillary line. It was diffuse and of a somewhat heaving character. The heart was markedly enlarged to percussion; the left border extended about 1 cm. beyond the anterior axillary line. The heart did not seem to be enlarged to the right. On auscultation the heart tones were very poor; both the first and second sounds were diminished in intensity. There was a suggestion of a gallop rhythm along the left sternal border; no murmurs nor adventitial sounds were demonstrable. The liver was palpable three fingers' breadth below the right costal border. Moderate pitting edema of both ankles was present.

The electrocardiogram (figure 1) showed a normal sinus rhythm with a rate of 115, P–R interval 0.16, QRS duration 0.10, right ventricular preponderance, QRS_1 notched, $QRS_{2 \text{ and } 3}$ slurred, Q_2 present, T_1 upright, $T_{2 \text{ and } 3}$ negative, $QRS_{4 \text{ and } 5}$ almost

† Further history obtainable from his physician, Dr. T. H. Rayburn of Pontotoc, Mississippi, was that in October, 1940, the patient was seen with a typical attack of coronary occlusion, characterized by severe pain in precordium, some dyspnea, and some nausea. His blood pressure was 100 mm. Hg systolic and 60 mm. diastolic, and his pulse was barely perceptible at about 100. The pain continued for several days and his disability to date.

entirely down, the first phase of Cf_2 being 1½ mm. in height, the first phase of Cf_4 being less than 1 mm. in height, S–T–T$_4$ and $_5$ normal.

On fluoroscopic and orthodiagraphic examination (figure 2) it was noted that there was moderate congestion in both hilar regions. The apices and the costophrenic angles were clear. The heart was markedly enlarged; this enlargement was of the aortic type, being mostly in the region of the left ventricle. The ratio of the transverse diameter of the heart to the thorax was 70 per cent. In the sagittal view of the chest there was evidence of enlargement in the region of the left ventricle. The aorta measured 3½ cm. in the left oblique view; this is just above the normal limit. Along the left border about 2 cm. above the apex there was a region in which
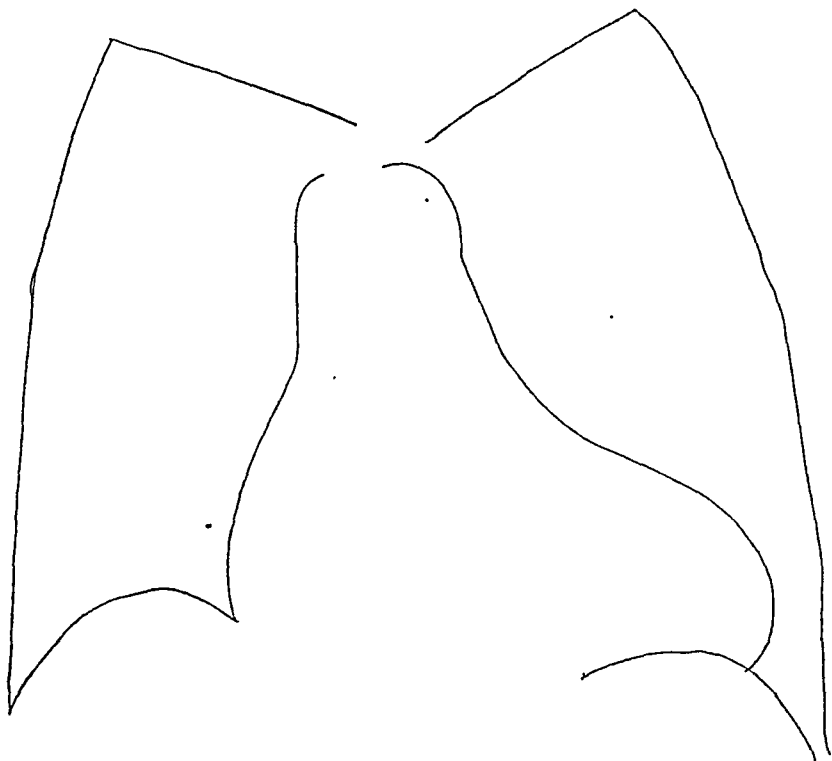
Fig. 2. Orthodiagram showing elongated apex and area of paradoxical pulsation.

there was no cardiac motility. With the patient turned slightly towards the left oblique diameter there was observed a slight outward bulging of this area with each contraction of the heart.

DISCUSSION

About 85 per cent of ventricular aneurysms follow cardiac infarction subsequent to the occlusion of a coronary artery.[3] The balance is made up of miscellaneous causes such as syphilis of the myocardium, or is of mycotic, rheumatic, congenital, and traumatic origin.

The pathological changes which occur in the production of a ventricular aneurysm are as follows: Subsequent to an occlusion of a coronary vessel there appears necrosis of the myocardium supplied by this vessel with replacement fibrosis. This weakened area then stretches with the production of a large or small aneurysmal dilatation, depending on the size of the area involved. This

may be saccular in outline, communicating with the ventricular cavity by a neck, or more often a bulge or out-pouching not sharply delineated from the ventricle. An aneurysm may be located in any part of the left ventricle; aneurysms of the right ventricle are very rare, but the most common site is the anterior wall, involving the apex or the left border just above the apex. Other less frequent sites are the posterior wall, base of the heart, or intraventricular septum.[3]

It has been suggested by Brams and Gropper[5] and Fulton[6] that inadequate bed rest predisposes to the formation of ventricular aneurysm, evidently because a firm scar is not allowed to form by the excessive cardiac load subsequent to early return to activity. In the present case the patient attempted to be up some three to four days following his occlusion and was never placed on strict, continuous rest in bed.

Clinically, there is nearly always a past history of coronary occlusion. This is usually clear, as in the case reported, although these aneurysms may occasionally follow a silent occlusion.[3] The length of time for its development varies. The average time of diagnosis in Parkinson and Bedford's[8] series was 17½ months after an occlusion, varying from three months to seven years. Aneurysms occurring a week or two after an occlusion have been reported.[7] In the case reported the diagnosis was made about two and one-half months after a coronary occlusion.   ·

Many signs have been mentioned as having diagnostic significance. Older writers were impressed mainly by such ausculatory findings as murmurs, both systolic and diastolic, and characterized as blowing or whistling, humming or musical. A gallop rhythm was suggestive of this condition to some. These auditory findings have failed to live up to their earlier promise.[1, 5, 3]

An enlarged heart is characteristic, but this alone is without significance unless it occurs in a patient who was previously known to have no cardiac condition that would explain this enlargement. This is true in the present case, and I believe this fact is corroborative evidence that an aneurysm existed in this report.

Pulsatory phenomena have been of great diagnostic significance. Libman and Sacks[8] in 1927 pointed out that a feeble first sound associated with a pulsation most marked between the apex and the sternum was very suggestive of a cardiac aneurysm. A systolic pulsation separate and distinct from the apex pulsation has been stressed by Strauch,[9] Libman and Sacks,[8] Parkinson, Bedford and Thompson.[8] Dressler[1] believes pulsatory findings are of the greatest significance. In his series of cases radiological examination was of help in only one-half of the series, whereas pulsatory phenomena were present in all. He describes these findings as follows: "The diagnosis of cardiac aneurysm is based primarily on physical examination. On palpation one finds a large and forceful cardiac thrust, which, depending upon the site of the aneurysm, is located either within the midclavicular line or outside of it, and most commonly at the level of the fifth rib. The diffuse character of the thrust, its considerable width, and particularly its medial extension, are significant features in diagnosis. The area of pulsation is likely to be situated more craniad than one would expect for the apical thrust caused by an hypertrophied left ventricle. Such a pulsation is of significance for the diagnosis of cardiac aneurysm, if the history and the electrocardiographic findings indicate a preceding cardiac infarction, and if other causes for such a forceful cardiac thrust, such as hypertension or mitral and aortic lesions, can be excluded."

In the present case the area of pulsation was diffuse and of a somewhat heaving character; it extended from the mesial to the midclavicular line to the anterior axillary line. This was in sharp distinction to the very weak heart sounds. Both the first and the second sounds here were equally diminished. Here, too, there was a gallop rhythm, but this is of questionable significance as the patient was in obvious decompensation.

To most men radiography, more especially fluoroscopy, offers the best means of accurately diagnosing cardiac aneurysm.[3, 5, 7, 10]

Parkinson et al.[3] give the following radiographic signs as being of diagnostic significance:

(1) Enlargement of the left ventricle with deformity of its contour.
(2) A localized protuberance inseparable from the heart shadow on rotation of the patient.
(3) Abnormal or absent pulsation of the aneurysmal zone.
(4) Evidence of adhesions between the heart and chest wall.
(5) Calcification of the wall of the sac or contained clot.

The heart is almost always enlarged. This enlargement is left ventricular in type and is of the so-called "aortic contour." The aneurysm most often involves the lower half of the left ventricle, which makes the apex appear broadened or blunted and gives the heart a square or rectangular appearance.[3] The most characteristic finding of aneurysm, when it is present, is an abnormal bulge projecting from the surface of the left ventricular border. This is particularly diagnostic if also there is one of three findings under the fluoroscope:

(1) A diminished or total lack of pulsation in the region of this bulge.
(2) A paradoxical pulsation in the region of this supposed aneurysm, i.e., a systolic expansion of this area.
(3) Calcification of the pericardium or wall of the aneurysm.

A straight anteroposterior view may fail to demonstrate an abnormality of the ventricular contour for several reasons. The aneurysm may grow directly forward [11] or directly backward.[3, 6] If located at the apex, this bulge may be buried in the diaphragm and thus be obscured. Again, the interventricular septum may be involved, and so there would be an internal rather than external aneurysm.[5, 12] For these reasons rotation of the patient into the various oblique positions under fluoroscopic control is invaluable and often will make the diagnosis a certainty, whereas it can only be suspected in the usual A–P radiograph. The right oblique view is best for demonstrating aneurysms of the anterior surface of the heart, the left for lesions on the posterior surface. Parkinson et al.[3] point out that they have been impressed by discrepancy between this enlarged left ventricle and a small vascular pedicle. In other causes of left ventricular hypertrophy, such as hypertension, a large left ventricle is most often associated with a broad pedicle from an unfolding of the aorta.

In the present report fluoroscopy and orthodiagraphy revealed a very greatly enlarged heart. This enlargement was mainly in the region of the left ventricle, which in the A–P view approached the lateral chest wall. The region of the apex was very much elongated. In this area there was a total absence of pulsation. With the patient turned very slightly in the left oblique view there was

seen in this region a slight outward bulging with each systolic contraction of the heart.

The electrocardiograph has been thought by many to give little diagnostic aid,[1, 3, 5, 6] being only of corroborative value in that it showed evidence of cardiac infarction and helped in the location of the area infarcted.

In 1938 Sigler and Schneid [10] pointed out that typical aneurysms seemed to be associated with major QRS deflections directed downward in the second and third lead with low voltage in Lead I. Nordenfelt [13] in 1939 made a study of electrocardiographic changes associated with ventricular aneurysms, collecting eight cases from the literature and reporting two of his own. He concluded "that large chronic aneurysms of the anterior wall of the ventricle often give the following electrocardiographic changes: Relatively low R_1, deep S_2, S_3, elevated S–T segments in all leads, negative T_1, and positive T_2, T_3. There is often also a Q_1. In four cases Lead IV was also included; in those cases R was absent and the S-wave was deep. The S–T segment was elevated and passed directly into a positive T-wave." He also found this was a relatively rare type of electrocardiogram, occurring only four times in 1300 tracings, and, apart from aneurysms, was found only with anterior infarcts in the process of healing. If persistent, it is always suggestive of cardiac aneurysm. Eliaser and Konigsberg [4] in the same year confirmed that this type of electrocardiogram was found in the presence of ventricular aneurysm, finding it in 40 per cent of their cases and in 35.3 per cent of cases reported in the literature. They also described a second type of electrocardiogram which, though rare in occurrence, was just as diagnostic as the above. In cases collected from the literature this was found in 23.5 per cent, whereas in their series it occurred in 40 per cent. This type of curve is described as showing marked right axis deviation with a negative T-wave in Lead I and an upright P in the same lead. These authors were unable to establish any correlation between the location of the aneurysm of the left ventricle and the axis deviation produced on the electrocardiogram. Aneurysms of the same site might produce any one of a number of electrocardiographic changes, namely (1) an S_1 type, (2) an $S_{2, 3}$ type, (3) bundle branch block, and (4) miscellaneous changes.

In the case reported the electrocardiogram was essentially similar to the S_1 type as reported by Eliaser and Konigsberg.[4] Here, however, T_1 was positive, whereas $T_{2 \text{ and } 3}$ were slightly negative. There was also a small Q-wave in Lead II.

The presence of right axis deviation in the electrocardiogram in a case with obvious left ventricular enlargement is interesting enough to deserve comment. It is rare to find right axis deviation in the presence of hypertensive or arteriosclerotic heart disease. Nathanson [14] found only slight right axis deviation in two cases out of a group of 50 with advanced coronary disease. White and Comeau,[15] in 200 cases of coronary artery disease, found only seven (3.5 per cent) to have right axis deviation, and here it was of a very slight degree. They concluded: "It is evident that the finding of right axis deviation is strong, though not conclusive, evidence that the patient does not have coronary heart disease."

Bohning and Katz [16] found right axis shift to be infrequent in coronary occlusion, occurring only in some cases of anterior infarction. McMillan and Bellet [17] state that "right axis deviation sometimes occurs after an anterior in-

farction." Klainer,[18] in a recent report, found only 36 instances of right axis deviation in hypertensive or arteriosclerotic heart disease in all the electrocardiographic records of the Beth Israel Hospital over a 10 year period (1929–1938). Of the 13 autopsied cases 12 showed severe coronary disease, and in 10 there were myocardial infarcts. In all of these cases showing infarcts there was extensive necrosis of the heart muscle of the left ventricle. In two other cases there was a diffuse fibrosis of the myocardium. The cause of this right axis deviation in the presence of left ventricular enlargement, Klainer believed, was due to the widespread necrosis of the left ventricle so interfering with the conduction system of the myocardium as to completely nullify the effects of hypertrophy of this ventricle. No mention is made in this article as to whether a ventricular aneurysm was present or not. However, if the necrosis of the myocardium was extensive, as the author states, it is highly probable that aneurysmal dilatation was present to a greater or lesser extent in some of his cases.

In view of the rarity of occurrence of right axis deviation in cases with hypertensive or arteriosclerotic heart disease and of its frequency (40 per cent of cases, Eliaser and Konigsberg [4]) in cardiac aneurysm, I believe this type of electrocardiogram is very suggestive of a cardiac aneurysm, and when it occurs unexpectedly in a case of otherwise unexplainable left ventricular enlargement the possibility of this diagnosis should be brought to mind.

The $S_{2,3}$ type, although also suggestive of ventricular aneurysm, occurs not infrequently in other conditions, such as non-sacculated myocardial infarcts, dilated hearts, and marked enlargement of the left ventricle.

As Eliaser and Konigsberg [4] point out, it is worthy of note that 63.7 per cent of cardiac aneurysms fall into one of two electrocardiographic patterns.

SUMMARY

1. A case of cardiac aneurysm is reported with clinical, radiological, and electrocardiographic findings.

2. No one method will diagnose every case, but the majority of cases can be diagnosed antemortem by the correlation of the above methods.

BIBLIOGRAPHY

1. DRESSLER, R.: Cardiac aneurysm: a report of ten cases, ANN. INT. MED., 1940, xiv, 100.
2. VILK, N. L., and RABINOVITCH, M. P.: Aneurysm of the heart due to syphilis, Russk. Klin., 1930, xiii, 280.
3. PARKINSON, JOHN, BEDFORD, D. E., and THOMPSON, W. A. R.: Cardiac aneurysm, Quart. Jr. Med., 1938, vii, 455.
4. ELIASER, MAURICE, JR., and KONIGSBERG, J.: Electrocardiographic findings in cases of ventricular aneurysm, Arch. Int. Med., 1939, lxiv, 493.
5. BRAMS, W. A., and GROPPER, A.: Cardiac aneurysm—an evaluation of its clinical features, Ill. Med. Jr., 1940, lxxviii, 246.
6. FULTON, M. N.: Aneurysm of the ventricle of the heart, Jr. Am. Med. Assoc., 1941, cxvi, 115.
7. SHOOKOFF, C., and DOUGLAS, A. H.: A case of acute coronary occlusion with roentgenological evidence of the early development of an aneurysm of the left ventricle, Am. Heart Jr., 1931, vii, 95.

8. LIBMAN, E., and SACKS, B.: A case illustrating the leukocytosis of progressive myocardial necrosis following coronary artery necrosis, Am. Heart Jr., 1927, ii, 321.

9. STRAUCH, quoted by PARKINSON ET AL.[3]: Cardiac aneurysm, Quart. Jr. Med., 1938, vii, 455.

10. SIGLER, L. H., and SCHNEID, R. J. J.: The diagnosis of cardiac aneurysm—report of two cases, ANN. INT. MED., 1935, viii, 1033.

11. EAST, T.: Two cases of aneurysm of left ventricle, Proc. Royal Soc. Med., 1932, xxvi, 518.

12. MALLORY, TRACY: Cabot Case Conference, Case No. 26312, New England Med. Jr., 1940, ccxxiii, 189.

13. NORDENFELT, ALOF.: The electrocardiogram in chronic aneurysm of the heart, Acta med. Scandin., 1939, cii, 101.

14. NATHANSON, M. H.: Electrocardiogram in coronary disease, Am. Heart Jr., 1930, v, 257.

15. COMEAU, W. J., and WHITE, P. D.: The clinical significance of right axis deviation in the electrocardiogram, Am. Heart Jr., 1939, xviii, 334.

16. BOHNING, A., and KATZ, L. N.: Four lead electrocardiogram in cases of recent coronary occlusion, Arch. Int. Med., 1938, lxi, 241.

17. McMILLAN, T. M., and BELLET, S.: Chapter on Electrocardiography, Stroud, Cardiovascular disease, Vol. 1, 1941, F. A. Davis Co., Philadelphia.

18. KLAINER, M. J.: The prognostic significance of right axis deviation in arteriosclerotic and hypertensive heart disease, Am. Jr. Med. Sci., 1940, cxcix, 795.

VISUALIZATION OF THE BILIARY TRACT WITH AIR AND BARIUM FOLLOWING A BARIUM MEAL *

By DANIEL B. FAUST, M.D., F.A.C.P., and CHARLES S. MUDGETT, M.D., F.A.C.P., *Washington, D. C.*

DURING studies made on the gastrointestinal tract, it has been noted from time to time that the gall-bladder or bile ducts, or both, contain air or barium. There has been much speculation about the cause of these occasional findings and an even greater interest as to the relationship between such findings and the symptoms presented by the patient. The cases reported are far from being identical and opinions differ greatly as to the cause.

In 1901, Stolz [1] reported three cases in which gas was found in the gall-bladder at autopsy. In 1925, Kirchmayr [2] reported an emphysematous cholecystitis diagnosed during a cholecystectomy. In 1927, Wahlberg [3] reported four cases of gas bacillus infection found in a thousand gall-bladder operations. He included two cases previously reported in 1923 by Brutt. In 1931, Hegner [4] reported a case of gaseous pericholecystitis due to gas bacillus infection. The primary pathological process was a chronic cholecystitis with stones.

Gabriel,[5] in 1930, reported proof of patency of the common bile ducts in a case operated upon twice. The first operation was cholecystectomy. The patient's general condition had not permitted the removal of the gall-bladder at the first operation, at which time the gall-bladder had contained much foul pus. A large stone was found in the common bile duct when the gall-bladder was finally removed. Patency was demonstrated by injection of lipiodol through a tube inserted into the ducts through the biliary fistula.

In 1931, Jenkinson and Brouse [6] reported two cases in which there was visualization of the bile ducts by barium administered for gastrointestinal study. They mentioned 10 such cases reported at that time, most of which were explained on the basis of intestinal fistulae between some part of the gastrointestinal and the biliary tract.

In 1933, Rees [7] reported a case of duodenocolic fistula with incompetent sphincter of Oddi. Traction from the fistulous tract apparently produced the incompetency, allowing the duodenal contents to pass into the bile ducts. The ramifications of the hepatic tree were visualized by a barium meal. Liver function was normal, but a non-functioning gall-bladder was demonstrated. An exploratory laparotomy was performed, revealing a fistula from the descending portion of the duodenum to the transverse colon. The fistula was dissected and removed. The gall-bladder was opened and gas escaped. Symptoms were relieved. However, a barium meal later still demonstrated patency of the sphincter of Oddi with barium filled bile ducts.

In 1936, Powers [8] reported four cases with air in the hepatic ducts. He states that air shadows in the hepatic tree probably occur quite frequently. It appears to be his impression that internal biliary fistulae were responsible for the findings in his cases. In 1938, Schmidt [9] reported a case of emphysematous cholecystitis. The gas-filled gall-bladder was shown on roentgen examination, without the use of dye. The cholecystogram showed poor gall-bladder function. This case was treated medically with improvement.

In 1921, Busi [10] reported two cases with the gall-bladder filled with barium and air, following a barium meal. In both cases there was a spontaneous biliary fistula between the gall-bladder and the duodenum, following a rupture of the gall-bladder, with passage of a biliary calculus directly into the duodenum.

In 1925, Berg [11] reported a case with air and barium in the gall-bladder after a barium meal, six years following a surgical anastomosis of the gall-bladder to the stomach for an unstated reason.

In 1926, Mallet [12] reported three cases in which both barium and air were present in the gall-bladder following a barium meal. The first was a case which had been operated upon for cholelithiasis and chronic pancreatitis, in which a surgical anastomosis had been performed between the gall-bladder and stomach three years previously. In his second case an anastomosis had been performed a month and a half previously between the gall-bladder and stomach because of obstructive jaundice caused by a tumor of the pancreas. In the third case, an anastomosis between the gall-bladder and stomach had been performed for the relief of painful abdominal crises. In this last case roentgenograms seven months later showed air in the gall-bladder, with barium in the region of the anastomosis.

Alberti,[13] in 1927, reported a case in which a fistulous tract had been formed between the duodenal bulb and the gall-bladder, following a periduodenal abscess subsequent to the perforation of a duodenal ulcer. Air and barium were seen in the fistulous tract, the gall-bladder and the intra- and extrahepatic bile passages following a barium meal.

In 1931, Gråberger [14] reported the case of a 70 year old female who had suffered from abdominal pain associated with eructations of gas for 30 years. An internal biliary fistula between the gall-bladder and the duodenal bulb was found, which was believed to have been caused by the passage of a calculus from

the gall-bladder into the duodenum. In this case the smaller biliary radicals in the liver were outlined with the barium, and air noted in the smaller biliary ducts in the liver. No air was seen in the gall-bladder.

Beutel,[15] in 1932, reported a case having adenocarcinoma, Grade IV, of the gall-bladder with cholelithiasis, and associated jaundice. There was a fistula between the gall-bladder and the duodenum, and air was noted in the gall-bladder. The patient died and the findings were confirmed.

Prévôt,[16] in 1933, reported a case in which there was a spontaneous biliary fistula between the gall-bladder and the hepatic flexure of the colon, caused by the direct passage of a stone from the gall-bladder to the colon. In this case, following a barium enema, the barium was seen in the fistulous tract, and both barium and air in the gall-bladder. Air was also noted in the common bile duct and the hepatic duct. Prévôt reported a second case the same year in which a gastrointestinal series showed barium in the gall-bladder and cystic duct, with air in the common bile duct, in a patient who had a spontaneous biliary fistula from the gall-bladder to the duodenum. This followed a direct passage of a stone from the gall-bladder into the duodenum.

In 1935, Podlasky [17] reported a case in which there had been interscapular pain, with vomiting for one year, and a period of similar type of pain lasting two months, 15 years previously. Films after a barium enema and a barium meal both showed barium and air in the gall-bladder. A fistula was demonstrated between the fundus of the gall-bladder and the hepatic flexure that had probably occurred as a result of the direct passage of a stone from the gall-bladder to the colon. Operation was performed, with the removal of the fistulous tract, and a stone from the gall-bladder. The patient died postoperatively.

In 1939, Pfeile [18] reported a case in which only air was seen in the gall-bladder. This patient had had a surgical anastomosis of the gall-bladder to the duodenum because of a carcinoma of the ampulla of Vater.

It will be noted that in these cases the appearance of air in the gall-bladder was due either to a gas bacillus infection of the gall-bladder, or to a fistulous communication from the biliary tract to the stomach, the duodenum, or the colon, either spontaneous or surgical in origin. Numerous instances are found in the literature in which the biliary tract in part or as a whole has been outlined with barium following a barium meal or a barium enema, but without air being noted in the biliary tract. In these cases spontaneous or surgical biliary fistulae were present in the great majority. In many instances there had apparently been a direct passage of a calculus from the gall-bladder to the duodenum, either the duodenal bulb, or the second portion of the duodenum, or to the colon, most commonly the hepatic flexure. Seventeen cases have been reported in which no fistulae were demonstrated, and in which the biliary tract was outlined with barium to a greater or lesser extent. In none of the cases without fistulae was there any air noted in the gall-bladder or the bile ducts. It is believed in these cases that the barium gained entrance into the biliary tract through an incompetent sphincter of Oddi, and perhaps this incompetency accounted for the symptoms in these cases.

The first reported case of this type was in 1921, when Stephenson [19] reported a case with epigastric pain, relieved by food, of 18 years' duration. A previous cholecystectomy and appendectomy had been performed. Again, in 1921, Beall and Jagoda [20] reported a case that had had epigastric pain, nausea and vomiting,

with chills and associated fever, for four months. There had been no previous operation. Exploration revealed an abscess in the left upper portion of the lesser peritoneal cavity, and enlargement of the pancreas was noted. In both of these cases there was visualization of the biliary tract with barium following a barium meal, but no fistulae were found.

In 1926, Fishbaugh[21] reported a case, with nausea and vomiting of a few months' duration, associated with loss of weight. The patient died and at autopsy a tumor of the pancreas was found obstructing the second portion of the duodenum. Sighinolfi,[22] in 1926, reported a case in which the chief symptoms had been epigastric pain, with nausea and vomiting for two to three years. No operations had been performed. No fistulae were demonstrated in either of these cases.

In 1929, Venable and Briggs[23] reported two cases in which there was visualization of the biliary tract without a fistula. The first complained of pain, vomiting, chills and fever. This patient had had a previous cholecystectomy, and operation subsequent to the examination was performed with removal of a calculus from a greatly distended common bile duct. The second case complained of pain, nausea and vomiting, with loss of weight. Previously a tumor, which had involved the greater curvature of the stomach, had been removed from the splenic flexure of the colon. Operation was again performed and a tumor mass involving the greater curvature of the stomach, the jejunum, the spleen, and the pancreas was found.

In 1929, Johannesson[24] reported two cases in which there was incompetency of the sphincter of Oddi. There had been no previous operations in these cases. A large calculus was removed from the common bile duct, in one case, and the gall-bladder was removed because of chronic cholecystitis in the other. In the latter case, the common bile duct was large and the walls thick.

In one of the cases mentioned by Jenkinson and Brouse,[6] in 1931, no fistula was demonstrated. It is assumed that there was incompetency of the sphincter of Oddi. This patient had had a cholecystostomy 17 years previously, later an appendectomy, removal of calculi from the pancreas, and an oöphorectomy. She had had jaundice four years previously, associated with pain in the right upper quadrant of the abdomen. No subsequent operation was performed.

In 1932, Pennington[25] reported a case that for one year had suffered from attacks of abdominal distention with nausea and vomiting, and loss of weight. Operation was performed, and a carcinoma of the pancreas, with moderate dilatation of the first portion of the duodenum and narrowing of the transverse portion of the duodenum, was found.

In 1934, Béclère and Porcher[26] reported a case with the common bile duct, cystic duct, part of the hepatic duct, and the gall-bladder visualized with barium, following a barium meal. There was marked antiperistalsis in the descending and ascending portions of the duodenum, and a fistula was not demonstrated.

In 1935, Levy et al.[27] reported a case with visualization of the extra-hepatic ducts and gall-bladder with barium, in a patient who had complained of epigastric pain for 10 years. Operation revealed a duodenal ulcer but there was no fistula.

In 1936, Titone[28] reported a case with epigastric pain, on whom previous gastroenterostomy had been performed. At operation a duodenal ulcer was found, with dilatation of the first and second portions of the duodenum.

In 1937, Wichtl[29] reported a case with pain in the right upper quadrant, chills

and fever one year previously. At operation a scar of a duodenal ulcer in the region of the ampulla of Vater was found. The scar was located on the anterior wall of the descending portion of the duodenum, the entire duodenum being infiltrated, and the posterior wall fixed to the pancreas. It was believed that the contraction of the scar distorted the ampulla of Vater so that the sphincter of Oddi became incompetent.

In 1938, Cristofanetti [30] reported four cases in which there was visualization

FIG. 1. · Gastrointestinal series, showing air, with a small amount of barium, in the gall-bladder.

of the biliary tract. In three cases fistulae were found, and in the fourth there was none. The chief complaint of this case was epigastric pain. The gall-bladder was not visualized with the dye, and a diagnosis of chronic cholecystitis was made.

In cases without fistulae, as with those with fistulae, the symptoms varied, but in most instances were referred to the upper abdomen. A variety of conditions was found in the cases with incompetency of the sphincter of Oddi, the most frequent being duodenal ulcer and tumors in the upper abdomen. No

definite conclusions can be drawn from this small group of cases. In the case we are reporting the findings cannot be explained by either a gas bacillus infection of the gall-bladder or a fistula between the biliary and gastrointestinal tracts. There was undoubtedly a relaxation of the sphincter of Oddi with general atony of the biliary tract. No case has been found in the literature in which the biliary tract has been visualized, and air seen in the gall-bladder without a fistula being present, as was in the case reported below.

FIG. 2. Fourteen-hour cholecystogram showing the dye and air in the gall-bladder.

CASE REPORT

E. J. M., male, aged 46 years, was admitted to Walter Reed General Hospital on December 26, 1939. His previous personal history was not remarkable until 1930. At that time, following symptoms of gaseous distention, burning epigastric pain before and one hour after eating, a diagnosis of gastric ulcer had been made. Following dietary measures in 1931, a gastrointestinal series showed no recurrence of the ulcer. Four years prior to admission he developed pain in the right upper quadrant associated with flatulence occurring in paroxysms. A cholecystogram in 1938 showed a non-

functioning gall-bladder without calculi. Symptoms had continued, but had been worse for a few weeks prior to admission. Ten days prior to admission he had had a severe attack of pain in the right upper quadrant with marked flatulence, and similar attacks almost daily for a week prior to admission. The pain radiated to the back and to the area below the right shoulder. The severity of the pain varied, but was
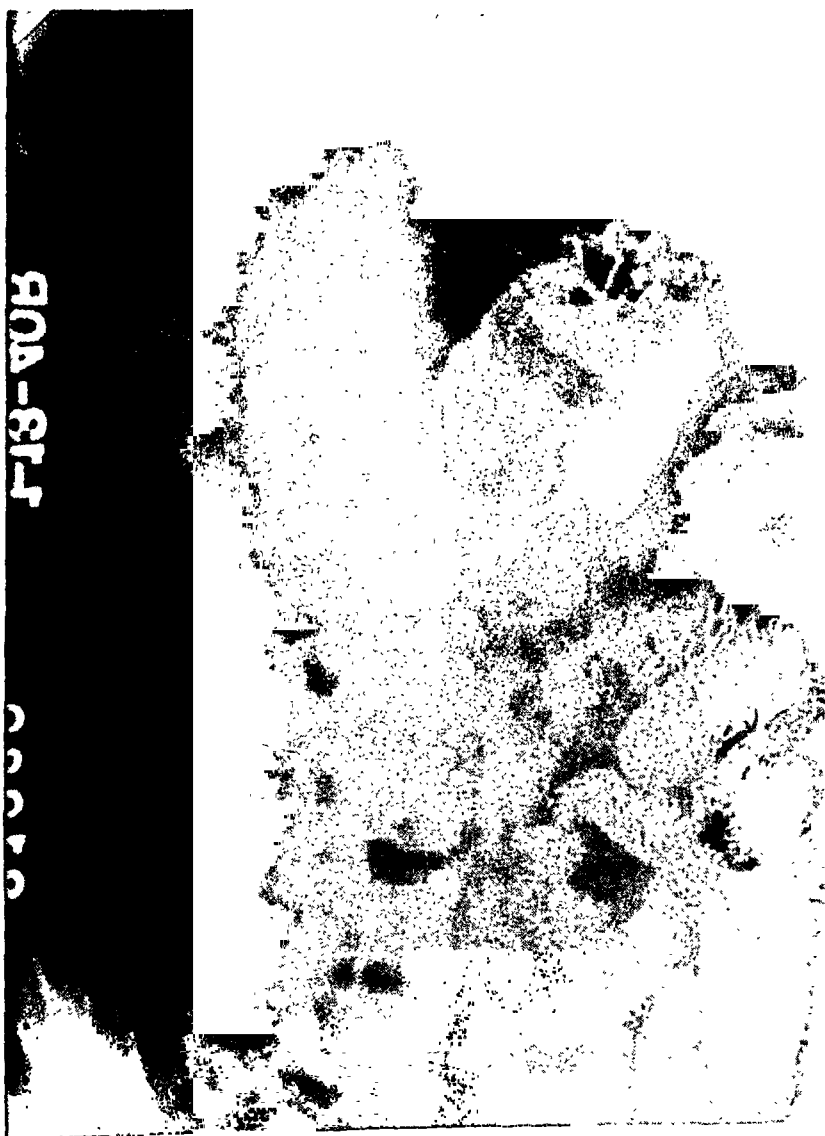
FIG. 3. Combined cholecystogram and gastrointestinal series, taken prior to operation, showing air and barium in the gall-bladder, and barium in the common bile duct, hepatic ducts and the smaller bile ducts in the liver.

often excruciating. It occurred most often when the stomach was empty, often waking the patient at night. The pain was relieved by alkalies, but best by milk. The pain frequently seemed to be brought on by beer or a fatty meal. There had been vomiting on only one occasion, and that occurred during a severe attack of pain 10 days prior to admission. There had been no nausea. The stools had occasionally been light in color, but not clay-colored at any time. He had been eating a moderately low fat diet for some months, and had drunk no alcoholic beverages.

Examination showed a well nourished adult male weighing 165 pounds. Aside from moderate tenderness in the upper right and lower left quadrants of the abdomen, the examination was normal.

Urinalyses and repeated blood counts were normal. The Kahn test was negative. The blood urea nitrogen rose to 33 mg. per 100 c.c., following the vomiting of about 200 c.c. of old and fresh blood on January 13, 1940. The creatinine was 2 mg.

FIG. 4. Combined cholecystogram and gastrointestinal series, taken prior to operation, showing the dye and air in the gall-bladder, and visualization of the biliary tree with barium.

per 100 c.c. The blood chlorides were normal. Six days after the hemorrhage from the gastrointestinal tract, the blood urea nitrogen had returned to normal. Proctoscopic examination was normal. Gastric fractional analysis showed a high terminal acidity. Repeated studies of the gastrointestinal tract following a barium meal, alone (figure 1), and combined with a cholecystogram (figures 2, 3 and 4) revealed a constant deformity of the second portion of the duodenum, associated with a reflux of

the opaque material into the common, cystic, hepatic and pancreatic ducts, and the gall-bladder. The gall-bladder was outlined by the dye, and showed a fluid level and the presence of air (figures 2 and 4). At six hours a small amount of barium remained in the gall-bladder and common ducts.

The cause of the findings was not determined, but it was felt that there might possibly be a duodenal ulcer, or a polyp in the second portion of the duodenum in the region of the sphincter of Oddi, which might account for its incompetency. Because of this possibility and the gastrointestinal hemorrhage, an exploratory laparotomy was

FIG. 5. Combined cholecystogram and gastrointestinal series, following operation, still showing visualization of the biliary tree with barium.

performed on January 17, 1940. The stomach was found to be normal. The duodenum was opened and explored for a distance of eight inches, and no polyp, tumor or ulcer was found. A large tube passed easily, without obstruction, through the first and second portions of the duodenum and no abnormalities were found. The gall-bladder was adherent to the second portion of the duodenum and was easily freed. No stones were palpable and the walls of the gall-bladder were not thickened. The common bile duct was easily palpated and no stones felt. The head of the pancreas was somewhat larger and firmer than normal, but a diagnosis of tumor of the head of the pancreas could not be made on gross appearance. Following operation a bland

diet was taken and symptoms improved. No further acute pain or distress was experienced.

On February 13, 1940, a combined cholecystogram and gastrointestinal series (figures 5 and 6) showed the same findings that were present prior to operation. The patient was discharged from the .hospital on February 19, 1940, and has continued to be free from acute pain and flatulence to date (April 30, 1940).

FIG. 6. Combined cholecystogram and gastrointestinal series at six hours, showing faint visualization of the gall-bladder with the dye, and a fleck of barium retained, and streaking of the intrahepatic ducts with barium, taken following operation.

COMMENT

The findings in the case reported were undoubtedly caused by incompetency of the sphincter of Oddi, with a general atony of the whole biliary tract. Traction from the cholecystoduodenal adhesions may have played a part in producing the incompetency of the sphincter of Oddi. Releasing the adhesions at operation followed by the use of a bland diet, low in fat, may in part explain the symptomatic relief afforded this patient.

SUMMARY

1. The literature on emphysema of the gall-bladder, and visualization of the biliary tract with barium following a barium meal, is briefly reviewed. Previously reported cases were explained on a basis of a cholecystitis due to gas bacillus infections, to internal biliary fistulae, or, as in the case reported, to incompetency of the sphincter of Oddi.

2. A case of emphysema of the gall-bladder with incompetency of the sphincter of Oddi, and general atony of the biliary tract, which was visualized following a barium meal, symptomatically relieved by the release of cholecysto-duodenal adhesions, and dietary measures postoperatively, is reported.

BIBLIOGRAPHY

1. STOLZ, A.: Ueber Gasbildung in den Gallenwegen, Virchow's Arch. f. path. Anat., 1901, clxv, 90–123.

2. KIRCHMAYR, L.: Ueber einen Fall von Gasbrand der Gallenblase, Zentralbl. f. Chir., 1925, lii, 1522.

3. WAHLBERG, K.: Die Gasbazilleninfektion der Gallenblase, München. med. Wchnschr., 1927, lxxiv, 2095.

4. HEGNER, C. F.: Gaseous pericholecystitis with cholecystitis, Arch. Surg., 1931, xxii, 993–1000.

5. GABRIEL, W. B.: Proof of patency of bile duct by injection of lipiodol, Lancet, 1930, i, 1014–1015.

6. JENKINSON, E. L., and BROUSE, I. E.: Visualization of bile ducts following administration of barium meal, Am. Jr. Surg., 1931, xii, 499–501.

7. REES, C. E.: Duodenocolic fistula with incompetent sphincter, Jr. Am. Med. Assoc., 1933, c, 491–497.

8. POWERS, ROBERT A.: Air in hepatic ducts, Radiology, 1936, xxvii, 474–478.

9. SCHMIDT, E. A.: Emphysematous cholecystitis and pericholecystitis, Radiology, 1938, xxxi, 423–427.

10. BUSI, A.: Reperti radiologici in due casi di fistola cisticoduodenale, Radiol. med., 1921, viii, 122.

11. BERG, H. H.: Über engste Verbindung von Röntgendurchleuchtung und Aufnahmeverfahren, Fortschr. a. d. Geb. d. Röntgenstrahlen, 1925, xxxiii, 25.

12. MALLET-GUY and BEAUPÈRE: Exploration radiologique des bouches de cholecystogastrostomie, Arch. d. mal. de l'app. digestif, 1926, xvi, 686.

13. ALBERTI, O.: Sopra alcune complicanze secondarie a perforazione di processi ulcerativi gastro-duodenale, Radiol. med., 1927, xiv, 729.

14. GRÅBERGER, G.: Beitrag fur Röntgendiagnose innerer Gallenfisteln, Acta radiol., 1931, xii, 164.

15. BEUTEL, A.: Karzinomatose Gallenblasenduodenalfistel, Röntgenpraxis, 1932, iv, 326.

16. PRÉVÔT, R.: Über innere Gallenwegfisteln, Röntgenpraxis, 1933, v, 177.

17. PODLASKY, H. B.: Biliary colic fistula, Radiology, 1935, xxiv, 345.

18. PFEILE, X., SCHINZ, DAENSCH, and FRIEDL: Lehrbuch der diagnostik Röntgenologie, 4th Edition, 1939, G. Thieme, Leipzig, 1963.

19. STEPHENSON, F. B.: Opaque meal in the liver ducts, Jr. Radiol., 1921, ii, 35–40.

20. BEALL, F. C., and JAGODA, S.: Injection of the bile ducts with barium, Jr. Am. Med. Assoc., 1921, lxxvi, 1483.

21. FISHBAUGH, E. C.: Chronic duodenal stagnation, Trans. Section Gastroenterology and Proctology, Am. Med. Assoc., 1926, 191.

22. SIGHINOLFI, P.: Riempimento opaco del coledoco e della cistifellea via retrograda durante un esame del tube digerente, Bull. delle Scienze Mediche, 1926, iv, 313.

23. VENABLE, J. F., and BRIGGS, P. J.: Visualization of bile ducts after an opaque meal, Guy's Hosp. Rep., 1929, lxxix, 123.
24. JOHANNESSON, C. J.: Cholecystography, Am. Jr. Roentgenol., 1929, xxii, 25.
25. PENNINGTON, W. E.: Patency of the ampulla of Vater, Jr. Indiana Med. Assoc., 1932, xxv, 375.
26. BÉCLÈRE, H., and PORCHER, P.: Anatomie radiologique des voies biliaires extra-hépatiques et du canal de Wirsung, Jr. radiol. et d'électrol., 1934, xviii, 209.
27. LEVY, M., WEYL, COTTENOT, and CHERIGIE: Remplissage spontane du choledoque et de la vesicule biliaire au cours de l'ingestion d'un repas opaque, Arch. d. mal. de l'app. digestif, 1935, xxv, 419.
28. TITONE, M.: Opacizzazione delle vie biliari extra e intrahepatiche con pasto baritato, Ann. di radiol. e fis. med., 1936, x, 210.
29. WICHTL, O.: Kontrastdarstellung der Gallenwege von der Papilla Vateri aus bei Ulcus Duodeni, Röntgenpraxis, 1937, ix, 559.
30. CRISTOFANETTI, P.: Sulle iniezioni spontanee con pasto opaco delle vie biliari, Quaderni di Radiologia, 1938, iii, 269.

EDITORIAL

HEPATITIS FOLLOWING THE ADMINISTRATION OF HUMAN SERUM

THE first clear recognition of the association of hepatitis and jaundice with the administration of supposedly normal human serum appears to have been made by Findlay and MacCallum,[1,2] who reported the development of this condition in men who had received yellow fever vaccine. They proved that the disease so produced was not yellow fever and that the active agent could have been conveyed only by the human serum used in the cultivation and preparation of the vaccine.

A little later Soper and Smith[3] reported the occurrence of similar cases in Brazil, and in 1940 Fox et al.[4] reported a second outbreak. A large proportion of the cases of jaundice was limited to those who received vaccine from three lots out of 265 which had been used during that period. As far as known these lots differed only in the source of the human serum used in their preparation.

A large number of similar cases also occurred in the armed forces of the United States in 1942.[5,6] The Secretary of War announced that 28,585 cases of jaundice occurred with 62 deaths in all. Here, too, jaundice occurred only after the administration of certain lots of vaccine, and it was believed that the noxious agent was introduced in the human serum.

In 1937, an outbreak of jaundice occurred in England among children who had received injections from one batch of pooled convalescent measles serum. Details of this epidemic have recently been published.[7] Of 109 cases treated with this lot, 41 developed hepatitis and eight died. A second batch of adult measles serum gave rise to at least 11 cases of hepatitis with one death. Although differing in some details, the disease so closely resembled that following yellow fever vaccine that it seems probable that a similar if not identical agent is concerned.

A brief reference[7] is also made to a similar apparently milder epidemic of 86 cases of jaundice which developed in 266 British troops after the administration of Seitz-filtered pooled mumps convalescent plasma.

One striking feature of all these outbreaks was the long incubation period. This ranged from 12 to 20 weeks in a large majority of the cases, with ex-

[1] FINDLAY, G. M., and MacCALLUM, F. O.: Note on acute hepatitis and yellow fever immunization, Trans. Roy. Soc. Trop. Med. and Hyg., 1937, xxxi, 297–308.

[2] FINDLAY, G. M., and MacCALLUM, F. O.: Hepatitis and jaundice associated with immunization against certain virus diseases, Proc. Roy. Soc. Med., 1938, xxxi, 799–806.

[3] SOPER, F. L., and SMITH, H. H.: Yellow fever vaccination with cultivated virus and immune and hyperimmune serum, Am. Jr. Trop. Med., 1938, xvii, 111–134.

[4] Fox, J. P. ET AL.: Observations on the occurrence of icterus in Brazil following vaccination against yellow fever, Am. Jr. Hyg., 1932, xxxvi, 68–116.

[5] Jaundice following yellow fever vaccination, editorial, Jr. Am. Med. Assoc., 1942, cxix, 1110.

[6] The outbreak of jaundice in the army, Circular letter No. 95, S. G. O., Jr. Am. Med. Assoc., 1942, cxx, 51–53.

[7] Homologous serum jaundice, Memorandum prepared by medical officers of the Ministry of Health, Lancet, 1943, i, 83–88.

tremes ranging from two weeks to over a year. In most other respects the disease was indistinguishable from ordinary infectious hepatitis (catarrhal jaundice), either in its clinical features or in the pathological lesions reported in the fatal cases.

The onset was usually gradual, with malaise, fatigue, loss of appetite and digestive disturbances; distention, epigastric distress, nausea, vomiting and diarrhea or constipation were frequently observed. Fever was slight and often absent. The urine became dark and the feces often light in color. Pruritus occasionally preceded the appearance of icterus. This was usually moderate in intensity and in a few cases failed to develop. The blood serum showed a high icterus index and gave usually a positive direct van den Bergh reaction.

In some cases there was pain and stiffness in the joints, and rashes appeared, urticarial in type or resembling erythema multiforme. In about 20 to 30 per cent of the cases the liver was enlarged and tender, but demonstrable enlargement of the spleen was rare. The leukocyte count was usually normal. Bromsulfalein retention was commonly observed during the acute stage in the cases so tested, but the excretion rate returned to normal with recovery.

In the children who had received measles convalescent serum, the disease was relatively severe and the mortality high. In the severe cases there was often restlessness, irritability, intractability with screaming or delirium, occasionally muscular rigidity with convulsions, or flaccidity; and disturbance of reflexes, including an extensor plantar response. These features suggest an associated encephalitis, although the spinal fluid was normal in the one case examined.

A majority of the cases recovered in from four to eight weeks, and recovery seems to have been complete. In the fatal cases, death usually occurred from three to six weeks after the onset of the illness with extreme limits in the yellow fever vaccine cases of 2 to 12 weeks. Four of the measles convalescent serum cases, however, died on the fourth, fifth, sixth and ninth days respectively. The mortality varied from 0.2 per cent in the U. S. Army cases and 2.4 per cent in the Brazilian cases of Fox et al., to 12 per cent in the small group receiving measles convalescent serum.

The principal autopsy finding was necrosis of the liver parenchymal cells, beginning in the center of the lobules and progressing in the extreme cases to the usual picture of acute yellow atrophy. Edema and acute inflammation of the gastrointestinal tract, particularly of the cecum, were mentioned in the American Army cases.

The etiology of the hepatitis is a question of great interest which has not yet been solved. Numerous attempts to isolate an infectious agent by culture and animal inoculation have been unsuccessful. Findlay and MacCallum suggested that the agent is a virus. This was based in part on the fact that it passed through a Seitz filter, that it perpetuated itself in the cultures of vaccine, and resisted inactivation (and in the case of the measles serum, treat-

ment with phenol and ether). Because of the clinical resemblance of post-vaccination jaundice to infectious hepatitis, they suggested that the latter disease is caused by a virus and that the serum used in preparing the vaccine may have come from a subclinical case of hepatitis (or possibly a carrier).

There is no direct proof of this hypothesis, nor is it known that infectious hepatitis is caused by a virus. No donor of icterogenic serum has been reported, who gave a history of jaundice. Three positive objections to this theory have been advanced. The incubation period of the two diseases is quite different. That of infectious hepatitis is believed to be usually between two and four weeks, whereas that of "serum jaundice" is as many months. The age incidence is also different. A majority of the cases of infectious hepatitis occur in children or adolescents under 16. In the Brazilian cases, however, adults were predominantly affected, and suffered a more severe form of the disease than did children.

Finally, if serum hepatitis is identical with infectious hepatitis, there should be contact infections in persons who had been exposed to cases of serum hepatitis. This has not been the experience either in Brazil or in the U. S. Army. Propert, however, has reported two cases of jaundice in contacts with cases of measles serum hepatitis. Furthermore Findlay and Martin [8] mention the occurrence of a disease indistinguishable from infectious hepatitis in African personnel in a unit in which they had been exposed to British troops with postvaccine jaundice.

Attempts have been made to convey infectious hepatitis to human volunteers, but the results have been conflicting. Thus Voegt [9] claims to have transmitted the disease to human volunteers by feeding duodenal contents and by injections of serum from patients in the preicteric stage. Lanier,[10] on the other hand, reported negative results in a similar series of experiments. Attempts to transmit the disease to animals have been almost invariably unsuccessful.

Findlay and Martin,[8] however, have recently reported transmission experiments in which they inoculated four volunteers intranasally with nasal washings from four cases of jaundice following yellow fever vaccine. After an incubation period of 28 to 50 days, a mild hepatitis developed in three of the four subjects. This observation, which appears to be dependable, confirms the view that a living agent is concerned, although it does not prove the identity of serum jaundice and infectious hepatitis.

This whole question is under active investigation, and a solution of many of these points may be anticipated. As far as vaccination against yellow fever is concerned, from the practical standpoint the difficulty has probably been met simply by discontinuing the use of human serum in preparing the vaccine.

    [8] FINDLAY, G. M., and MARTIN, N. H.: Jaundice following yellow fever immunization. Transmission by intranasal instillation, Lancet, 1943, i, 678–680.
    [9] Voegt, quoted by Findlay and Martin.[8]
    [10] Lanier, quoted by Fox et al.[4]

The cases of jaundice which were first recognized all followed the use of serum for purposes of immunization. This is doubtless merely because their epidemic occurrence arrested attention and made it relatively easy to find a common factor which could explain their origin. There is no reason to doubt that cases of jaundice would occur if blood from such donors were used for ordinary transfusions or for the preparation of pooled plasma or serum. The long interval of two to six months before the development of the jaundice would divert suspicion from the transfused blood as a cause of the illness unless the possibility of such a relationship were known to the observer. The first clearly recognized cases of this type were reported from a British hospital.[7] Of 36 patients receiving massive transfusions of Seitz-filtered dried human serum in the treatment of peripheral vascular disease, eight developed jaundice. Conditions were such that ordinary infectious hepatitis could be excluded. Beeson[11] has also reported seven cases of jaundice occurring one to four months after transfusions of blood or plasma. Six of these occurred among a group of 81 persons diagnosed as catarrhal jaundice or toxic hepatitis.

With the current widespread use of plasma, cases of this type are certain to develop. Prevention at present is a difficult problem, as no experimental animal is known to be susceptible to the agent. A preliminary trial of each lot of pooled plasma in a small group of human subjects would presumably determine its safety. Because of the long period of observation, however, such a procedure would scarcely be practicable under field conditions. Fortunately the incidence of such cases is small, the mortality is low and recovery appears to be complete. The risk involved is too small to restrict the use of blood or plasma in any conditions in which it is needed.

[11] BEESON, P. B.: Jaundice occurring one to four months after transfusion of blood or plasma, Jr. Am. Med. Assoc., 1943, cxxi, 1132–1134.

REVIEWS

Dermatologic Therapy in General Practice. Second edition. By MARION B. SULZ-
BERGER, M.D., and JACK WOLF, M.D. 632 pages; 21 × 14.5 cm. Year Book
Publishers, Chicago. 1942. Price, $5.00.

This book is intended primarily for general practitioners, and the authors give a
clear, concise expose of the commoner diseases of the skin. In addition to the gen-
eral principles of therapy, the authors give detailed formulae for many of the diseases
and indicate how the substances are to be used. There are a few photographs illus-
trating methods of therapy and skin lesions which are quite helpful.

Although the title of this book is "Dermatologic Therapy," the authors include
in it a chapter on syphilis. Since any scheme for the treatment of syphilis must at
present be tentative and incomplete, because ideas and methods are changing as a
result of current research, the chapter is satisfactory, although necessarily brief. The
book as a whole can be highly recommended for general practitioners and students
entering practice.

<div align="right">H. M. R.</div>

Occupational Diseases of the Skin. By LOUIS SCHWARTZ, M.D., and LOUIS TULIPAN,
M.D. 799 pages; 24 × 15.5 cm. Lea and Febiger, Philadelphia. 1939. Price,
$10.00.

Since occupational diseases have been recognized by almost all states in the
Union as a cause for compensation, numerous articles and symposia on the subject
have been published. The culmination of these may be found in this book by Schwartz
and Tulipan, in which the authors have thoroughly reviewed the entire subject and
have included essentially all the ordinary occupations and their hazards.

Among the more timely chapters are those on dermatoses caused by explosives
and war gases. Seventy-four occupations have been investigated, the ingredients of
the various materials used in these occupations have been enumerated, and the prob-
ability of their being hazards is discussed. This volume is essentially a Bible for
those who are interested in industrial diseases. The principal fault to be found is that
many of the photographs are poor and might well have been omitted. This book
should be useful to all those who are interested in the workmen's compensation laws,
especially industrial dermatologists.

<div align="right">H. M. R.</div>

BOOKS RECEIVED

Books received during June are acknowledged in the following section. As far
as practicable, those of special interest will be selected for review later, but it is not
possible to discuss all of them.

Whooping Cough. By JOSEPH H. LAPIN, B. Chem., M.D. 238 pages; 23.5 × 15 cm.
1943. Charles C. Thomas, Springfield, Illinois. Price, $4.50.

Managing Your Mind. By S. H. KRAINES, M.D., and E. S. THETFORD. 374 pages;
22 × 15 cm. 1943. The Macmillan Company, New York City. Price, $2.75.

Nutritional Deficiency in Nervous and Mental Disease. Volume XXII of Research
Publications of the Association for Research in Nervous and Mental Disease.
Editorial Board: STANLEY COBB, M.D. (Chairman), EDWIN F. GILDEA, M.D.,
and HARRY M. ZIMMERMAN, M.D. 215 pages; 23.5 × 15.5 cm. 1943. The
Williams & Wilkins Company, Baltimore. Price, $4.00.

Human Gastric Function. By STEWART WOLF, M.D., Captain, M.C., A. U. S., and HAROLD G. WOLFF, M.D. With a foreword by WALTER B. CANNON, M.D. 195 pages; 24 × 16 cm. 1943. Oxford University Press, New York City. Price, $4.75.

Pain Mechanisms. By W. K. LIVINGSTON, Lieutenant Commander, M.C., U.S.N.R. 253 pages; 22 × 15 cm. 1943. The Macmillan Company, New York City. Price, $3.75.

Diagnosis of Uterine Cancer by the Vaginal Smear. By GEORGE N. PAPANICOLAOU, M.D., and HERBERT F. TRAUT, M.D. 73 pages; 28.5 × 21 cm. 1943. The Commonwealth Fund, New York City. Price, $5.00.

COLLEGE NEWS NOTES

Already published in preceding issues of this journal were the names of 1,439 Fellows and Associates of the College on active military duty. Herewith are reported the names of 14 additional members, bringing the grand total to 1,453.

Sidney Adler
Walter S. Burrage
F. Benjamin Carr
John T. Eads
Clarence K. Elliott
Thomas B. Magath
Cornelius C. Perrine

Norman Plummer
David E. Quinn
William F. Rexer
Bernard M. Scholder
Frank E. Smith, Jr.
Solomon C. Werch
I. Sidney Zaur

Captain Milton M. Portis, Medical Corps, California State Guard, has been retired to inactive duty.

GIFTS TO THE COLLEGE LIBRARY

We gratefully acknowledge receipt of the following gifts to the College Library of Publications by Members:

Books

Dr. James B. Herrick, M.A.C.P., Chicago, Ill.—"A Short History of Cardiology."

Reprints

Edward L. Bortz, F.A.C.P., Commander, (MC), U. S. Naval Reserve—8 reprints;
George R. Callender, F.A.C.P., Colonel, (MC), U. S. Army—1 reprint;
Dr. Pedro Leandro Farinas Mayo, F.A.C.P., Havana, Cuba—1 reprint;
Dr. Hyman I. Goldstein (Associate), Camden, N. J.—1 reprint;
Dr. Isidore W. Held, F.A.C.P., New York, N. Y.—3 reprints;
Walter S. Jensen, F.A.C.P., Colonel, (MC), U. S. Army—1 reprint;
Henry J. John, F.A.C.P., Lieutenant Colonel, (MRC), U. S. Army—4 reprints;
Dr. Charles E. Lyght, F.A.C.P., New York, N. Y.—2 reprints;
Dr. Berthold S. Pollak, F.A.C.P., Jersey City, N. J.—1 reprint;
Dr. Adolph Sachs, F.A.C.P., Omaha, Nebr.—16 reprints;
Dr. Charles H. Sprague, F.A.C.P., Bridgeport, Conn.—1 reprint;
Dr. J. Manuel Viamonte, F.A.C.P., Havana, Cuba—1 reprint.

DR. ELLIOTT P. JOSLIN AWARDED DISTINGUISHED SERVICE MEDAL OF THE AMERICAN MEDICAL ASSOCIATION

Dr. Elliott P. Joslin, F.A.C.P., Boston, was the recipient of the Distinguished Service Medal Award of the American Medical Association for 1943 in recognition of his contribution to our knowledge of diabetes and as an educator in that field. Dr. Joslin is Honorary President of the American Diabetes Association. In 1932 he was the recipient of the Kober Medal of the Association of American Physicians. He has travelled throughout the nation extending instruction on diabetes to the medical pro-

fession and to the public. He has delivered various important lectures, such as the Harvey Society Lecture in Boston, the Stephen Walter Ranson Lecture of Northwestern University Medical School, and the Malthe Lectures.

Other recipients of the Distinguished Service Medal of the American Medical Association have included Dr. Rudolph Matas (1938), Dr. James B. Herrick, M.A.C.P., (1939), Dr. Chevalier Jackson (1940), Dr. James Ewing (1941). and Dr. Ludvig Hektoen (1942).

Dr. T. Grier Miller, F.A.C.P., Philadelphia, Professor of Clinical Medicine at the University of Pennsylvania School of Medicine, was recently honored by his Alma Mater, the University of North Carolina, by having bestowed upon him the honorary degree of Doctor of Laws.

Dr. Charles L. Brown, F.A.C.P., Professor of Medicine at Temple University School of Medicine, Philadelphia, was recently appointed by the American Society for Clinical Investigation as a member of that society's committee serving on the National Research Council.

Dr. Samuel E. Munson, F.A.C.P., Springfield, Ill., was honored at a dinner on June 10, 1943, marking his fifty years in the practice of medicine. The Sangamon County Medical Society Bulletin states that this is a distinction to which only 290 doctors out of 12,500 in Illinois have become eligible.

Dr. Munson was born August 25, 1866, attended Valparaiso University and graduated in medicine from Northwestern University Medical School in 1893. He did postgraduate work at' the University of Göttingen in Germany and at the University of Vienna. He has been in practice in Springfield, Ill., since 1899. He has been a Fellow of the American College of Physicians for many years, was one of the original members of its Board of Governors and served as a Vice President in 1941–42. He is a Diplomate of the American Board of Internal Medicine. He has served as President of the Illinois State Medical Society, as President of the Central District Medical Society, as President of the Sangamon County Medical Society, and he was for many years District Councillor of the Illinois State Medical Society.

Dr. Josiah J. Moore, F.A.C.P., Chicago, Ill., has been elected Treasurer of the American Medical Association to succeed Dr. Herman L. Kretschmer, who was made President-Elect at the Annual Meeting of the House of Delegates in June.

Dr. Ernest E. Irons, F.A.C.P., Chicago, Ill., was reëlected a Trustee of the American Medical Association for a term of five years.

Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, addressed a meeting of the Tenth and Eleventh Councillor Districts of the Medical Society of the State of Pennsylvania in Washington, Pa., June 17, 1943. Dr. Kelly spoke on "The Concept of Nutrition and Its Application Under War Rationing."

The New York Academy of Medicine will conduct its 16th Graduate Fortnight, October 11–22, 1943. The subject of this meeting will be "Disorders of the Digestive Tract." Among the speakers who will present papers at the scientific sessions are:

Dr. Andrew C. Ivy, F.A.C.P., Chicago, Ill.—The Ludwig Kast Lecture, "The Physiology of the Gastrointestinal Tract";

Dr. J. Arnold Bargen, F.A.C.P., Rochester, Minn.—"Present Status of Regional Enteritis and Ulcerative Colitis";

Thomas T. Mackie, F.A.C.P., Lieutenant Colonel, (MRC), U. S. Army—
"Amebiasis and the Flagellate Diarrheas";

Dr. W. Osler Abbott, F.A.C.P., Philadelphia, Pa.—"The Management of Acute
Intestinal Obstruction."

Dr. Harold G. Wolff, F.A.C.P., New York, N. Y., will be Chairman of a panel
discussion on "Emotions and Gastric Function" and Dr. Walter A. Bastedo, F.A.C.P.,
New York, N. Y., Chairman of a panel discussion on "Use of Sulfonamides in Gastro-
intestinal Diseases."

Dr. Arthur F. Chace, F.A.C.P., is President and Dr. Mahlon Ashford, F.A.C.P.,
Secretary of the New York Academy of Medicine. Dr. Bernard S. Oppenheimer,
F.A.C.P., is Chairman of the Committee on Medical Education of the Academy that
will arrange the program and Dr. F. Warner Bishop, F.A.C.P., is Chairman of the
Graduate Fortnight Committee.

The Kansas City Southwest Clinical Society will hold its 21st Annual Fall Clinical
Conference, October 4–6, 1943. Among the guest speakers who will present papers
at this conference are:

Dr. Harrison F. Flippin, F.A.C.P., Philadelphia, Pa.;
Dr. Edward H. Rynearson, F.A.C.P., Rochester, Minn.;
Dr. Tom D. Spies, F.A.C.P., Birmingham, Ala.;
Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Mich.;
Dr. Paul D. White, F.A.C.P., Boston, Mass.

The Mississippi Valley Medical Society will hold its 9th annual meeting in
Quincy, Ill., September 29–30, 1943. Among the well-known clinicians who have
accepted places on the program are:

Henry L. Dollard, F.A.C.P., Captain, (MC), U. S. Navy;
Dr. Willis M. Fowler, F.A.C.P., Iowa City, Iowa;
Dr. Samuel F. Haines, F.A.C.P., Rochester, Minn.;
Dr. Archibald L. Hoyne, F.A.C.P., Chicago, Ill.;
Dr. Robert W. Keeton, F.A.C.P., Chicago, Ill.;
Dr. LeRoy H. Sloan, F.A.C.P., Chicago, Ill.

Dr. Louis Hamman, F.A.C.P., Baltimore, Md., presented the Mellon Lecture
sponsored annually by the Society for Biological Research of the School of Medicine
of the University of Pittsburgh on May 27, 1943. Dr. Hamman spoke on "Acute
Diffuse Interstitial Fibrosis of the Lungs."

Dr. Burrell O. Raulston, F.A.C.P., has been appointed Dean and Professor of
Bacteriology at the University of Southern California School of Medicine in Los
Angeles to succeed Dr. Seeley G. Mudd, F.A.C.P., who has resigned. Dr. Raulston
has been Professor and Head of the Department of Medicine and Director of Clinical
Teaching at the University since 1930.

Dr. Robert S. Berghoff, F.A.C.P., Chicago, Ill., was recently elected one of the
Vice Presidents of the Illinois State Medical Society.

Dr. Floyd L. Rogers, F.A.C.P., Lincoln, Nebr., has been named President-Elect
of the Nebraska State Medical Association.

Dr. Peter Irving, F.A.C.P., New York, N. Y., Secretary of the Medical Society of the State of New York, has been named a member of the Moreland Act Commission by Governor Dewey. This commission will formulate a long range program for the improvement of the mental hygiene hospitals of the State of New York.

Dr. William H. Sebrell, Jr., F.A.C.P., U. S. Public Health Service, Bethesda, Md., has been named Treasurer of the American Institute of Nutrition.

Dr. Newton S. Stern, F.A.C.P., Memphis, Tenn., spoke on "Heart Neurosis" at the 81st semiannual meeting of the First Councilor District Medical Society of Northeast Arkansas at Jonesboro, May 27, 1943.

Dr. Newton G. Evans, F.A.C.P., Professor and Head of the Department of Pathology and a member of the Board of Trustees of the College of Medical Evangelists, Los Angeles, Calif., was unanimously elected Dean of the College, May 5, 1943.

Zolton T. Wirtschafter (Associate), Major, (MRC), U. S. Army, spoke on "The Importance of Minerals in Human Nutrition" at the 2nd Annual Conference on Conservation, Nutrition and Human Health held in Tar Hollow, Ohio, June 26–27, 1943.

The Aero Medical Association of the United States recently elected its first group of twenty-five Fellows in Aviation Medicine. Among the members of the College who were named Fellows of the Association are:

Harry G. Armstrong, F.A.C.P., Colonel, (MC), U. S. Army;
Dr. Louis H. Bauer, F.A.C.P., Hempstead, N. Y.;
Otis O. Benson, Jr. (Associate), Colonel, (MC), U. S. Army;
Leon D. Carson (Associate), Commander, (MC), U. S. Navy;
John R. Poppen, F.A.C.P., Captain, (MC), U. S. Navy;
Eugen G. Reinartz, F.A.C.P., Brigadier General, (MC), U. S. Army.

The new constitution and by-laws of the Aero Medical Association of the United States provide for the nomination of an initial group of ten Fellows and for the election of fifteen additional Fellows which shall comprise the first group. The by-laws further provide that all subsequent elections to Fellowship shall be made by the Group of Fellows and shall be by selection only from those who have made outstanding contributions to aviation medicine, and that not more than ten shall be elected to Fellowship during any one year.

On April 5, 1943, Dr. Marcos Fernan-Nunez, F.A.C.P., Milwaukee, Wis., spoke on "War Problems in Tropical Diseases" before the combined medical staffs of Army General Hospital No. 17 and the Post General Hospital of Camp McCoy, Wis.

Dr. Andrew C. Ivy, F.A.C.P., Dr. Italo F. Volini, F.A.C.P., Dr. Aaron Arkin, F.A.C.P. and Dr. Frederick Steigmann (Associate), all of Chicago, have been named members of the Board of Trustees of the Hektoen Institute for Medical Research of Cook County (Ill.).

Under the Presidency of Dr. Ernest D. Hitchcock, F.A.C.P., Great Falls, the Medical Association of Montana held its 65th Annual Session in Billings, July 7–8, 1943. Among the speakers were:

Dr. Wayne Gordon, F.A.C.P., Billings—"Gastritis: Diagnosis and Clinical Significance";

Alexander P. Ormond, F.A.C.P., Major, (MRC), U. S. Army—"The Wartime Spread of Communicable Diseases."

The Philadelphia Chapter of the National Foundation for Infantile Paralysis is sponsoring a series of eight lectures for physicians, nurses and physical therapists. One of these lectures will be presented by Dr. Pascal F. Lucchesi (Associate), Philadelphia. Dr. Lucchesi will speak on "Diagnostic Signs."

Under the direction of Dr. Malcolm T. MacEachern, F.A.C.P., Chicago, Ill., the 11th Chicago Institute for Hospital Administrators will be held August 30–September 10, 1943.

On May 14, 1943, Dr. C. Sidney Burwell, F.A.C.P., Dean of the Harvard Medical School, Boston, Mass., delivered the 6th Annual Gerrish Library Lecture at the Central Main General Hospital, Lewiston, Maine. Dr. Burwell spoke on "Changing Viewpoints as to Disorders of Circulation."

Dr. William H. Sebrell, Jr., F.A.C.P., U. S. Public Health Service, Bethesda, Md., delivered the Marcus A. Rothschild Lecture at Beth Israel Hospital, New York, N. Y., June 15, 1943. Dr. Sebrell spoke on "Trend of Recent Research in Vitamins and Clinical Symptoms of Vitamin Deficiency."

Dr. Lyell C. Kinney, F.A.C.P., San Diego, Calif., was elected a Vice President of the American College of Radiology at its annual meeting in Chicago, Ill., June 6, 1943.

The Vancouver Medical Association conducted its summer school in Vancouver, B. C., June 22–25, 1943. Among the speakers were:

Jonathan C. Meakins, F.A.C.P., Brigadier, Royal Canadian Army Medical Corps —"Effort Syndrome and Allied Conditions in Civil and Military Practice";

Dr. Maxwell M. Cantor, F.A.C.P., Edmonton, Alta.—"The Clinical Application of Research in Nutrition."

Dr. Wm. deB. MacNider, F.A.C.P., Chapel Hill, N. C., Kenan Research Professor of Pharmacology and Head of the Department of Pharmacology of the University of North Carolina School of Medicine, has relinquished the Headship of this Department, to become effective September 1, 1943. He will continue in the Department as a research professor.

Dr. Chester M. Kurtz, F.A.C.P., Associate Professor of Medicine, University of Wisconsin Medical School and Dr. N. C. Gilbert, Professor of Medicine, Northwestern University Medical School, were the special guest speakers at a meeting of the Rock County (Wisconsin) Medical Society at Janesville, June 22. The subject was

"Rheumatic Heart Disease and Coronary Heart Disease," with special emphasis on the convalescent care of cardiac cases.

The National Foundation for Infantile Paralysis announced, on July 2, twenty-eight grants, totaling $354,370.00, to universities, hospitals, laboratories and other institutions in eleven States to continue investigative work in this disease. The funds are raised annually in January through the celebration of President Roosevelt's birthday.

Sixteen grants, totaling $216,020.00, were made for virus and after-effects research. Four of these are long-term projects being conducted at Yale University, Johns Hopkins University, the University of Michigan and the University of Wisconsin.

Twelve grants, totaling $138,350.00, were made for various educational programs, including the training of technicians in the Kenny method of treatment. Some of these grants include projects for educational work for physicians and the public. $2,500.00 was appropriated for the preparation of a complete bibliography on poliomyelitis.

Dr. A. B. Brower, F.A.C.P., Dayton, College Governor for Ohio, will be the official representative of the American College of Physicians at the celebration of the one hundredth anniversary of Western Reserve University School of Medicine, to be held at Cleveland, October 27, 1943.

Dr. Walter Clarke, F.A.C.P., Executive Director of the American Social Hygiene Association, New York City, has been appointed Clinical Professor of Public Health Practice at Harvard University. During the past three years, he has served as Lecturer on Public Health Administrative Practice, as applied to the control of syphilis and gonorrhea, giving ten lectures on this subject each year at the Harvard School of Public Health. In the academic year 1943–44, he will give forty hours of instruction covering the course, diagnosis and treatment of syphilis, gonorrhea, lymphogranuloma venereum, granuloma inguinale and chancroid and the epidemiologic and administration measures for the control of these infections. He will also supervise the field training of the students of public health specializing in venereal disease control.

Dr. Clarke will continue as the Executive Director of the American Social Hygiene Association.

SPECIAL NOTICES

MEDICAL OFFICERS NEEDED FOR FEDERAL CIVILIAN WAR SERVICE

The critical shortage of physicians to engage in vital war work in the civilian branches of the Government continues. The great need for these men resulted in the announcing of a liberalized civil-service examination for Medical Officers in 1941. The Civil Service Commission has just revised and re-announced this examination.

The twenty optional branches under which doctors may apply range from General Practice to Aviation Medicine. Those appointed will perform professional duties as doctors of medicine in active practice in hospitals, in dispensaries, or in the field or in rural areas; or in bureaus of the Government such as the Veterans Administration, Civil Aeronautics Administration, Public Health Service, and Food and Drug Administration. Doctors will also be used in industrial establishments under direction of the War Department.

Applicants for all grades must have received the degree of M.D from an accredited medical school. Applicants for the Senior Medical Officer grade ($5,228

a year) must have had at least 5 years of appropriate medical experience; for the Medical Officer grade ($4,428 a year), 3 years of experience in addition to a required interneship; and for the Associate Medical Officer grade ($3,828), 1 year of interneship. The salaries quoted include overtime pay.

There are no written tests and no age limits. Persons now using their highest skills in war work should not apply for these positions. Appointments in Federal positions are made in accordance with War Manpower policies and employment stabilization plans. Before a definite offer of appointment is made, eligibles are cleared through the Procurement and Assignment Service for Physicians, Dentists, and Veterinarians, of the War Manpower Commission.

Persons .rated eligible on the Medical Officer examination of 1941 need not file applications again unless they consider that they now possess qualifications for eligibility in a higher grade or different option.

Further information and application forms may be obtained at first- and second-class post offices, Civil Service Regional Offices, and the Commission in Washington, D. C.

FORT DES MOINES, IOWA, June 19.—Marking a milestone in the recognition of women in medicine, an official ceremony was conducted this morning at First WAAC Training Center, Fort Des Moines, Ia. Dr. Eleanor Gutman and Dr. Elizabeth Garber became Officers in the Medical Corps of the Army of the United States, Dr. Gutman as a Captain and Dr. Garber as a First Lieutenant. They are the second and third ranking women in the Corps, Maj. Margaret Craighill being the first ranking.

Serving with the Women's Army Auxiliary Corps at First WAAC Training Center, first in the capacity of contract surgeons and then as Women's Army Auxiliary Corps Officers, the women physicians have been associated closely with the WAAC almost since its beginning.

The official ceremony took place in the Post Headquarters office with Maj. E. R. Payne, Post Adjutant, administering the oath of office.

Both Officers have had the rank of Second Officer which is the WAAC rank equivalent to First Lieutenant in the Army.

A Chinese blood bank, opened June 7 at 154 Nassau Street, New York City, to seek blood donations for soldiers of the Chinese armies, will accept the blood of persons who have had malaria, according to its sponsor, the American Bureau for Medical Aid to China. This can be done by using the Seitz filter, which eliminates malaria microörganisms.

Almost every Chinese has had malaria at some time in his life, and the sponsors of the project realized that there could be few Chinese donors to the blood bank if persons who had suffered from the disease were ruled out. Dr. John Scudder of Presbyterian Hospital, who as Chairman of the Blood Bank Committee of ABMAC has been largely responsible for carrying through the project, had tested and proved the efficacy of the filter in Puerto Rico.

Blood donations received at the bank are converted in its own laboratories into dry plasma and shipped to China in American army planes. The medical staff members of the blood bank, all of whom are Chinese, have had special training in American hospitals for this work and eventually will go to China as a unit to set up the first blood bank there.

OBITUARIES

DR. ARTHUR CONKLIN BRUSH

Dr. Arthur Conklin Brush, F.A.C.P., New York, N. Y., died on March 17, 1943, in the Methodist Hospital in Brooklyn of broncho-pneumonia, at the age of eighty years.

Dr. Brush was born in Brooklyn in 1862, attended the Polytechnic Institute, received the Degree of Doctor of Medicine from Columbia University College of Physicians and Surgeons in 1884. For many years he was a Visiting Neurologist and Consultant in the Kings County Hospital, Brooklyn Eye and Ear Hospital, Coney Island Hospital, and House of St. Giles the Crippled.

He had been retired from active practice for a number of years although he continued some medico-legal work for some years after his retirement. He was the author of numerous papers, was an Affiliate Fellow of the American Medical Association; Member of the Kings County Medical Society, Medical Society of the State of New York, New York Neurological Society, Brooklyn Pathological Society, Society of Medical Jurisprudence, and a Fellow of the American College of Physicians since 1920.

Dr. Brush was one of the last of the Old School, a highly respected citizen of the community, and his passing is a distinct loss to the medical profession and to his friends.

ASA L. LINCOLN, M.D., F.A.C.P.,
Governor for Eastern New York

DR. HUGH ATLEE BEAM

Dr. Hugh Atlee Beam, F.A.C.P., Moline, Ill., was born July 15, 1882, at Dakota City, Iowa. He graduated from Northwestern University Medical School in 1903. Thereafter he practiced medicine in Iowa for three years and then removed to Moline, Ill., where he developed an extensive practice, which he kept up until the time of his death.

Dr. Beam did graduate work at Glen Lake Sanitorium, near Minneapolis. He was a past President of the Rock Island County (Ill.) Medical Society and of the Iowa State Medical Society, and a member of the State Medical Legislative Committee and of the Trudeau Society. For eight years he was Medical Director of the Rock Island County Tuberculosis Sanitorium.

Dr. Beam died March 30, 1943, following an operation on the cervical spine at St. Luke's Hospital, St. Louis, aged sixty. He was a most highly respected physician and counsellor to the sick and to people in distress. Thousands of people in this community will mourn his passing.

WILLIAM F. SCHROEDER, M.D., F.A.C.P.,
Rock Island, Ill.

DR. FRANK R. BORDEN

Lt. Col. Frank R. Borden, (MC), U. S. A. (Retired), Fellow of the American College of Physicians, died in the Veterans Administration Facility at Augusta, Ga., March 28, 1942, of pneumonia, aged 68 years.

Colonel Borden was born in Wisconsin, November 1, 1874. He studied Pharmacy at Northwestern University, graduating in 1896, Ph.G. He received his medical degree in 1902 from the University of Illinois College of Medicine. Thereafter he served as Health Officer at Plainfield, Wis., and as local Surgeon to the Minneapolis, St. Paul and S. St. Marie Railroad. He served one year, 1907, as Instructor in Pharmacology at the College of Physicians and Surgeons of Milwaukee. On June 13, 1917, he entered the Medical Reserve Corps of the U. S. Army as First Lieutenant, serving during World War I, and remaining in the Corps after the War. He did postgraduate study at the University of Dijon (France) in 1919, and in 1924 graduated as a Flight Surgeon from the School of Aviation Medicine of the U. S. Army. For several years he served as Assistant Commandant and Director of the Extension Course of the School of Aviation Medicine. In 1937 he was retired from active duty, because of physical disability. He maintained Fellowship in the American Medical Association, and had been a Fellow of the American College of Physicians since 1936.

DR. WILLIAM HARRIS FUNK

Dr. William Harris Funk, F.A.C.P., Captain, (MC), U. S. Navy, died January 7, 1943, following twenty-two years in Naval Service.

Captain Funk was born at South Bend, Ind., May 14, 1893; received his A.B. degree from Williams College in 1916 and his M.D. degree from Johns Hopkins University School of Medicine in 1920. He immediately entered the Medical Corps of the Navy, and thereafter served on many assignments in various parts of the world where the Navy maintains its stations. In the course of his career he did postgraduate work not only at the U. S. Naval Medical School at Washington, D. C., but at the University of Pennsylvania Graduate School of Medicine in Philadelphia and the Massachusetts General Hospital in Boston.

He was a Diplomate of the National Board of Medical Examiners and of the American Board of Internal Medicine, a Fellow of the American Medical Association, and had been a Fellow of the American College of Physicians since 1931.

DR. CHARLES F. GORMLY

Dr. Charles Francis Gormly died June 26, 1943, at Providence.

A native of Providence, where he practiced internal medicine for thirty-two years, Dr. Gormly has brought to a close one of the most valuable medi-

cal careers in the history of Rhode Island. He was graduated from Tufts Medical School in 1909 and spent three years on the neurological and medical services at the Boston City Hospital. During the first World War he served with the British Army and later in the Army of the United States in which he held the rank of Major and was Physician-in-Chief of the 13th Evacuation Hospital in France. It was he who did practically all the ground work in the organization of the 68th Evacuation Hospital which was recruited from the staff of the Rhode Island Hospital and is now serving in India.

After many years as Visiting Physician Dr. Gormly four years ago became Physician-in-Chief of the Medical Service at the Rhode Island Hospital. Just before his death he completed a most successful year as President of the State Medical Society—a year which he brought to completion by an exhibition of sheer pluck that will be long remembered by his colleagues.

A number of signal honors came to him in his last few years. He was always a most enthusiastic member of our College and a regular attendant at its sessions. Many will remember him as the genial Chairman and Toastmaster at the first New England Regional Meeting of the College when, it was later discovered, he was already beginning to suffer from the condition of which he died about a year and a half later.

After thirty-three years of intimate friendship and association with Dr. Gormly the writer finds it impossible adequately to express his thoughts and feelings but will quote from his own contribution to the Rhode Island Medical Journal. "The value of his life to his friends and colleagues, to his casual acquaintances, indeed to every citizen of Rhode Island, is beyond our ability to estimate.

"Throughout the thirty-one years of his active practice he has always been a dynamic force for the betterment of the condition of his patients, his medical associates, his hospital and his community. Up to the time of his death he preserved a cheerful optimism and a clear-sighted interest in the planning of a future in which he knew he could not share.

"Always, even in the face of inevitable physical suffering and disaster his ready wit and glowing humor never failed. For almost a year and a half, as was generally known, he suffered the progressive inroads of an incurable malady and yet he carried on undaunted as practitioner, consultant and physician-in-chief and in addition brought to a most successful conclusion his year as President of the Rhode Island Medical Society.

"The courage with which he fought this campaign through equals the most heroic deeds for which men are decorated on the field of battle. He is a life-long inspiration to us all."

<div style="text-align:right">ALEX. M. BURGESS,
Governor for Rhode Island</div>

DR. ROY MUNRO COLLIE

Dr. Roy Munro Collie (Associate), Schenectady, N. Y., died April 24, 1943, of hypertensive heart disease, at the age of 59 years.

Dr. Collie was born at Gloversville, N. Y., graduated from the Albany Medical College in 1906, and for a great many years was connected in various capacities with the Ellis Hospital at Schenectady. His was a life time of service in that community. He was a member of the Schenectady Academy of Medicine, the New York State Medical Society, the Schenectady County Medical Society, and a Fellow of the American Medical Association. He had been an Associate of the American College of Physicians since 1926, having first become a member of the former American Congress on Internal Medicine in 1920. When that organization was merged with the College, he automatically was made an Associate and maintained that membership to the time of his death.

POSTGRADUATE COURSES BY THE AMERICAN COLLEGE OF PHYSICIANS, AUTUMN, 1943

The following courses have been arranged through the generous coöperation of the Directors and the institutions at which the courses will be given. The Advisory Committee on Postgraduate Courses will plan other courses during the winter and spring of 1944. These courses are organized especially for Fellows and Associates of the College, but where facilities are available, courses will be open to those with adequate preliminary training, including Medical Officers of the Armed Forces, who are now preparing either to meet the requirements for membership in the College or certification by the American Board of Internal Medicine.

The courses are made available by the College to its members at minimum cost, because the College assumes the expenses of promotion, advertising, printing and registration. Physicians on active duty in the Armed Forces will be granted free tuition.

COURSE NO. 1—ENDOCRINOLOGY
(October 11–16, 1943)

UNIVERSITY OF ILLINOIS COLLEGE OF MEDICINE AND THE PRESBYTERIAN HOSPITAL

1753 W. Congress St., Chicago, Ill.

WILLARD O. THOMPSON, M.D., F.A.C.P., *Director*

Fee, $20.00

OFFICERS OF INSTRUCTION

Fuller Albright, M.D., Associate Professor of Medicine, Harvard Medical School, Boston, Mass.

Percival Bailey, M.D., Professor of Neurosurgery, University of Illinois College of Medicine.

Anton J. Carlson, M.D., F.A.C.P., Professor of Physiology, Emeritus, University of Chicago, The School of Medicine.

Lester R. Dragstedt, M.D., Professor of Surgery, University of Chicago, The School of Medicine.

Carl Hartman, Ph.D., Professor and Head of the Department of Zoology and Physiology, University of Illinois.

Norris J. Heckel, M.D., F.A.C.S., Assistant Professor of Urology, University of Illinois College of Medicine.

Charles R. Huggins, M.D., Professor of Surgery (Genito-Urinary), University of Chicago, The School of Medicine.

Andrew C. Ivy. M.D., F.A.C.P., Professor of Physiology, Northwestern University Medical School.

Robert W. Keeton, M.D., F.A.C.P., Professor of Medicine and Head of the Department, University of Illinois College of Medicine.

A. T. Kenyon, M.D., Associate Professor of Medicine, University of Chicago, The School of Medicine.

F. C. Koch, Ph.D., Professor of Biochemistry, Emeritus, University of Chicago.

Carl R. Moore, Ph.D., Professor and Head of the Department of Zoology, University of Chicago.

J. deJ. Pemberton, M.D., F.A.C.S., Professor of Surgery, University of Minnesota Medical School; Head of Section in Surgery, Mayo Clinic; Rochester, Minn.

Edward H. Rynearson, M.D., F.A.C.P., Assistant Professor of Medicine, University of Minnesota Medical School; Consultant in Medicine, Mayo Clinic; Rochester, Minn.

Elmer L. Sevringhaus, M.D., F.A.C.P., Professor of Medicine, University of Wisconsin Medical School, Madison, Wis.

David Slight, M.D., Professor of Psychiatry, University of Chicago, The School of Medicine.

Willard O. Thompson, M.D., F.A.C.P., Associate Professor of Medicine, University of Illinois College of Medicine.

Rollin T. Woodyatt, M.D., Professor of Medicine, University of Illinois College of Medicine.

Wherever possible in this course in Endocrinology, all clinical discussions will be illustrated by the demonstration of patients.

In the preclinical sciences, discussion will be amplified by the presentation of actual specimens, by lantern slides and by microscopic demonstration.

All meetings will be held in one of the amphitheaters in the Presbyterian Hospital (1753 W. Congress St.). Arrangements will be made for luncheons at the *Illini* Union (715 S. Wood St.).

All those desiring to take the course are urged to make their hotel reservations early, because of the great demand for accommodations.

OUTLINE OF COURSE

Monday, October 11.

Some Significant Milestones in Our Understanding of the Endocrines.
    Dr. Carlson.
Endocrine Clinic: Diseases of the Thyroid.
    Dr. Thompson.
Ketosis and Diabetes: Present Status of the Problem.
    Dr. Woodyatt.
Principles Involved in the Treatment of Diabetes Mellitus.
    Dr. Keeton.

Tuesday, October 12.

Endocrine Treatment of Cancer of the Prostate.
    Dr. Huggins.
Endocrine Clinic: Hypogonadism.
    Dr. Thompson.
Influence of Sex Hormones on Spermatogenesis; Technique of Spermatozoa Counts; Evaluation of Sex Hormones in the Treatment of Obstruction at the Neck of the Bladder.
    Dr. Heckel.
Hormone Assays in Blood and Urine: Clinical Significance and Practical Application.
    Dr. Koch.
Pineal Disorders; Surgery of the Pituitary.
    Dr. Bailey.
Lipocaic and Fat Metabolism.
    Dr. Dragstedt.

Wednesday, October 13.

Dwarfism and Primary Ovarian Deficiency.
Dr. Kenyon.
Endocrine Disturbances Related to Deformations of the Genital Apparatus.
Dr. Ivy.
Endocrine Regulation of Menstruation: Clinical Significance.
Dr. Hartman.
Endocrine Clinic: Hypogonadism (Continued).
Dr. Thompson.

Thursday, October 14.

The Development of the Ovary and Testis: Clinical Application.
Dr. Moore.
Endocrine Clinic: Diseases of the Adrenals, with Special Reference to Addison's Disease.
Dr. Thompson.
Diseases of the Parathyroids.
Dr. Albright.
Psychotic Episodes in Endocrine Disorders.
Dr. Slight.

Friday, October 15.

Endocrine Clinic: Pituitary Disorders.
Dr. Thompson.
Some New Clinical Syndromes.
Dr. Albright.
Diseases of the Pituitary.
Dr. Rynearson.
Carcinoma of the Thyroid.
Dr. Pemberton.
Endocrine Disturbances of the Female Reproductive System.
Dr. Sevringhaus.

Saturday, October 16.

This day will be devoted to the Regional Meeting of the American College of Physicians at the Drake Hotel, Chicago, representing the States of Wisconsin, Iowa, Illinois, Indiana and Michigan. Detailed program later.

COURSE NO. 2—ALLERGY
(October 25–30, 1943)

ROOSEVELT HOSPITAL, NEW YORK, N. Y.

ROBERT A. COOKE, M.D., F.A.C.P., *Director*

(Minimal Registration, 25; Maximal Registration, 50)

Fee, $20.00

OFFICERS OF INSTRUCTION

Robert A. Cooke, M.D., F.A.C.P., Attending Physician and Director, Department of Allergy, Roosevelt Hospital.
Horace S. Baldwin, M.D., Assistant Professor of Clinical Medicine, Cornell University Medical College; Assistant Attending Physician and Chief of the Allergy Clinic, New York Hospital.

Aaron Brown, M.D., Assistant Clinical Professor of Medicine and Chief of Allergy Clinic, New York University College of Medicine; Assistant Visiting Physician, Bellevue Hospital.

Robert Chobot, M.D., F.A.C.P., Assistant Professor of Clinical Pediatrics, New York Post-Graduate Medical School and Hospital, Columbia University; Chief of Pediatric Allergy, New York Post-Graduate Medical School and Hospital; Assistant Chief, Allergy Clinic, Roosevelt Hospital.

Russell Clark Grove, M.D., Associate Surgeon, Otolaryngology, Roosevelt Hospital.

Joseph Harkavy, M.D., Associate in Medicine, Columbia University College of Physicians and Surgeons; Associate Physician and Chief of Allergy Clinic, Mt. Sinai Hospital; Associate Physician, Montefiore Hospital.

Selian Hebald, M.D., Assistant Chief of Allergy Clinic, Roosevelt Hospital; Senior Clinical Assistant in Allergy, Outpatient Department, Mt. Sinai Hospital.

Michael Heidelberger, Ph.D., Associate Professor of Biochemistry, Columbia University College of Physicians and Surgeons; Chemist, Presbyterian Hospital.

Beatrice Kesten, M.D., Dermatologist, Presbyterian Hospital and Vanderbilt Clinic; Associate Dermatologist, Welfare Hospital for Chronic Diseases.

Paul Klemperer, M.D., Pathologist, Mt. Sinai Hospital.

Will Cook Spain, M.D., F.A.C.P., Assistant Professor of Clinical Medicine, New York Post-Graduate Medical School and Hospital, Columbia University; Chief of Allergy Clinic and Attending Physician, New York Post-Graduate Medical School and Hospital.

Arthur Stull, Ph.D., Captain, U. S. Army Sanitary Corps.

Marion Sulzberger, M.D., Commander, (MC), U.S.N.R.

Albert Vander Veer, M.D., Consultant in Allergy and Chief of Allergy Clinic, Roosevelt Hospital.

Matthew Walzer, M.D., Associate in Medicine, Cornell University Medical College; Attending in Allergy and Chief of Allergy Clinic, Jewish Hospital, Brooklyn.

To make this course available to a larger group than formerly, it was decided to resort to the more didactic type of presentation with lectures, clinics and conferences. While the course is to be given at the Roosevelt Hospital, the Officers of Instruction have been drawn from many medical schools and hospitals throughout the City. All phases of Allergy—immunological, pathological and clinical—will be covered, including theoretical and practical aspects with the idea of furnishing the internist, the general practitioner or allergist with the latest information. On the last morning (October 30) there will be an optional session devoted to the preparation of allergen extracts and vaccines, and practical experience in testing.

OUTLINE OF COURSE

Monday, October 25.

A.M.

9:00–11:30   Registration.
Introduction to Allergy.
Dr. Cooke.

11:30– 1:00   Extracts: Methods of Preparation and Standardization.
Dr. Spain.

P.M.

2:00– 4:00   Skin Tests.
Dr. Walzer.

4:00– 6:00   Seasonal Hay Fever (1st session).
Dr. Vander Veer.

Tuesday, October 26.

    A.M.

9:00–11:00   Pediatric Allergy.
           Dr. Chobot.

11:00– 1:00   Vasomotor Rhinitis.
           Dr. Brown.

    P.M.

2:00– 4:00   Seasonal Hay Fever (2nd session).
           Dr. Vander Veer.

4:00– 6:00   Immunology.
           Dr. Heidelberger.

Wednesday, October 27.

    A.M.

9:00–11:00   Atopic Asthma.
           Dr. Spain.

11:00– 1:00   Pathology.
           Dr. Klemperer.

    P.M.

2:00– 4:00   Sinus Disease in Relation to Allergy.
           Dr. Grove.

4:00– 6:00   Infective Asthma.
           Dr. Cooke.

8:30   Conference.
           (All members).

Thursday, October 28.

    A.M.

9:00–11:00   Asthma—Differential Diagnosis, Serum, Drug and Insulin Allergy.
           Dr. Baldwin.

11:00– 1:00   Vascular Allergy, Menier's Disease, Migraine, Physical Allergy.
           Dr. Harkavy.

    P.M.

2:00– 3:00   Seasonal Hay Fever—Special Features.
           Dr. Hebald.

3:00– 5:00   Miscellaneous Allergies.
           Dr. Cooke.

Friday, October 29.

    A.M.

9:00–11:00   Contact Dermatitis.
           Dr. Sulzberger.

11:00– 1:00   Eczema, Urticaria, Angioneurotic Edema.
           Dr. Kesten.

    P.M.

2:00– 5:00   Clinic.
           Dr. Cooke.

8:00   Dinner and Roundtable.

Saturday, October 30.

    A.M.

9:00   Optional—Practical Work on Tests, Extracts, etc.
           Dr. Stull, et al.

Reading List and Bibliography

Course No. 2

An attempt is made to obtain reading lists for each Postgraduate Course for publication in the Annals of Internal Medicine, making these lists available to the entire membership of the College, in addition to preparing better the men who will take the courses. These lists are not to be considered as all-inclusive.

Textbooks

Practice of Allergy. Warren T. Vaughan. C. V. Mosby Co., St. Louis, 1939.

Asthma and Hay Fever in Theory and Practice. A. F. Coca, M. Walzer and A. A. Thommen. Charles C. Thomas, Baltimore, 1931.

Clinical Allergy. Louis Tuft. W. B. Saunders Co., Philadelphia, 1937.

Occupational Diseases of the Skin. Louis Schwartz and Louis Tulipan. Lea and Febiger, Philadelphia, 1939.

Monographs

Allergy. C. E. Von Pirquet. Archives of Internal Medicine 7: 259, 1911.

Anaphylaxis, Hypersensitiveness and Allergy. W. W. C. Topley. An Outline of Immunity, Chapter 12, p. 192. Wm. Wood Co., 1935.

Hypersensitiveness, Anaphylaxis, Allergy. H. Gideon Wells. The Chemical Aspects of Immunity, Chapter 9, p. 225, second edition. Chemical Catalog Co., New York, 1929.

Diseases of Allergy. Robert A. Cooke. Chapter 21, p. 1079, Internal Medicine. John H. Musser. Lea and Febiger, Philadelphia, 1938, third edition.

Diseases of Allergy. Robert A. Cooke. Page 535, A Textbook of Medicine. Russell L. Cecil. W. B. Saunders Co., Philadelphia, 1940, fifth edition.

Human Sensitization. Robert A. Cooke and A. Vander Veer. Journal of Immunology 1: 201, 1916.

Herter Lectures. H. H. Dale. Bulletin Johns Hopkins Hospital 31: pps. 257, 310, 373, 1920.

Anaphylaxis. Carl A. Dragstedt. Physiol. Rev. 21: 563, 1941.

Histamine and Anaphylaxis. W. Feldberg. Annual Review of Physiology, March 1941.

Articles

Immunological Basis of Sensitization

Horse Asthma Following Blood Transfusion. M. A. Ramirez. J. A. M. A. 73: 984, 1919.

Studies on the Reactions of Asthmatics and on Passive Transference of Hypersusceptibility. Arent de Besche. Am. J. Med. Sciences 166: 265, 1923.

Indirect Method of Testing. M. Walzer. J. Allergy 1: 231, 1930.

Studies in Hypersensitiveness. XXXVI. A Comparative Study of Antibodies Occurring in Anaphylaxis, Serum Disease and the Naturally Sensitive Man. Robert A. Cooke and W. C. Spain. J. Immunol. 17: 295, 1929.

Passive Sensitization of Human Skin by Serum of Experimentally Sensitized Animals. W. B. Sherman, A. Stull and S. F. Hampton. J. Immunol. 36: 447, 1939.

Serological Evidence of Immunity with Co-existing Sensitization in a Type of Human Allergy. Hay Fever. R. A. Cooke, J. H. Barnard, S. Hebald and A. Stull. J. Exper. Med. 62: 773, 1935.

Immunological Studies of Pollinosis. I. The Presence of Two Antibodies Related to the Same Pollen Antigen in the Serum of Treated Hay Fever Patients. M. H. Loveless. J. Immunol. 38: 25, 1940.

Studies in the Transmission of Sensitization from Mother to Child in Human Beings. S. D. Bell and Z. Eriksson. J. Immunol. 20: 447, 1931.

The Placental Transmission of Antibodies in the Skin-Sensitive Type of Human Allergy. W. B. Sherman, S. F. Hampton and R. A. Cooke. J. Exper. Med. *72:* 611, 1940.

The Question of the Elimination of Foreign Protein (Eggwhite) in Woman's Milk. H. H. Donnally. J. Immunol. *19:* 15, 1930.

The Production in the Rabbit of Hypersensitive Reactions to Lens, Rabbit Muscle and Low Ragweed Extracts by the Action of Staphylococcus Toxin. E. L. Burky. J. Allergy *5:* 466, 1934.

General Clinical Allergy

History Taking in Allergic Diseases. F. M. Rackemann. J. A. M. A. *106:* 976, 1936.

Studies in Specific Hypersensitiveness. III. On Constitutional Reactions: The Dangers of the Diagnostic Cutaneous Test and Therapeutic Injection of Allergens. R. A. Cooke. J. Immunol. *7:* 119, 1922.

The Occurrence of Constitutional Reactions in the Treatment of Hay Fever and Asthma: Analysis of the Causative Factors. F. F. Furstenberg and L. N. Gay. Bull. Johns Hopkins Hospital *60:* 412, 1937.

The Delayed Type of Allergic Reaction. R. A. Cooke. Ann. Int. Med. *3:* 658, 1930.

Treatment of Allergic Disorders with Histamine and Histaminase. H. L. Alexander. J. Lab. & Clin. Med. *26:* 110, 1940.

Asthma

Asthma in Children. R. A. Cooke. J. A. M. A. *102:* 664, 1934.

Infective Asthma. Indication of Its Allergic Nature. R. A. Cooke. Am. J. Med. Sci. *183:* 309, 1932.

Relation of Asthma to Sinusitis with Special Reference to the Results from Surgical Treatment. R. A. Cooke and R. C. Grove. Arch. Int. Med. *56:* 779, 1935.

The Pathology of Bronchial Asthma. H. L. Huber and K. K. Koessler. Arch. Int. Med. *30:* 689, 1922.

Effects on Heart of Long Standing Bronchial Asthma. H. L. Alexander, D. Luten and W. B. Kountz. J. A. M. A. *88:* 882, 1927.

Deaths from Bronchial Asthma. W. B. Kountz and H. L. Alexander. Arch. Path. *5:* 1003, 1928.

Studies in Specific Hypersensitiveness. IV. New Etiologic Factors in Bronchial Asthma. R. A. Cooke. J. Immunol. *7:* 147, 1922.

Asthma Due to a Fungus-Alternaria. J. G. Hopkins, R. W. Denham and B. M. Kesten. J. A. M. A. *94:* 6, 1930.

Nasal Allergies

Seasonal Hay Fever and Asthma Due to Molds. S. M. Feinberg. J. A. M. A. *107:* 1861, 1936.

Importance of Allergy in Etiology and Treatment of Nasal Mucous Polyps. R. A. Kern. J. A. M. A. *103:* 1293, 1934.

The Preparation and Standardization of Pollen Extracts for the Treatment of Hay Fever. R. A. Cooke and A. Stull. J. Allergy *4:* 87, 1933.

New Plan for Applying Specific Treatment of Pollen Hay Fever (Perennial Treatment). Aaron Brown. J. Immunol. *13:* 273, 1927.

The Relative Merits of Seasonal and Perennial Treatment of Hay Fever. A. Vander Veer. J. Allergy *7:* 578, 1936.

Calculating Pollen Concentration of the Air. E. C. Cocke. J. Allergy *8:* 601, 1937.

Evaluation of the Ragweed Hay Fever Resort Areas of North America. O. C. Durham. J. Allergy *8:* 175, 1937.

Intestinal Allergy

Gastrointestinal Manifestations of Allergy. R. A. Cooke. Bull. N. Y. Acad. Med. Second Series *IX:* 15, 1933.

Food Idiosyncrasy as a Factor of Importance in Gastro-enterology and in Allergy. W. T. Vaughan. Rev. Gastroenterol. *5:* 1, 1938.

Skin Allergy

A Tentative Classification of Allergic Dermatoses. M. B. Sulzberger, F. Wise and J. Wolf. J. A. M. A. *104:* 1489, 1935.

A Critical Review of 170 Cases of Urticaria and Angioneurotic Edema Followed for a Period of from Two to Ten Years. A. I. Fink and L. N. Gay. J. Allergy *5:* 615, 1934.

Eczema. L. W. Hill. Vol. IV., Chapter 43, Brenneman's Practice of Pediatrics. W. F. Prior Co., Hagerstown, Md.

Studies in Specific Hypersensitiveness. XXVII. Dermatitis Venenata: Toxicodendron Radicans. W. C. Spain and R. A. Cooke. J. Immunol. *13:* 93, 1927.

Report of the Investigation and Successful Treatment (Preventive) of Dermatitis Resulting from the Handling of Tulip Bulbs. A. H. W. Caulfeild. J. Allergy *8:* 181, 1937.

Miscellaneous Allergy

Cerebral Symptoms Induced by Angioneurotic Edema. F. Kennedy. Arch. Neurol. and Psychiat. *15:* 28, 1926.

Allergic Migraine. W. T. Vaughan. J. A. M. A. *88:* 1983, 1927.

Food Allergy in Henoch's Purpura. H. L. Alexander and C. H. Eyermann. Arch. Dermat. & Syph. *16:* 332, 1927.

The Clinical Diagnosis of Periarteritis Nodosa. M. B. Cohen, B. S. Kline and A. M. Young. J. A. M. A. *107:* 1555, 1936.

Allergy Induced by Immunization with Tetanus Toxoid. R. A. Cooke, S. F. Hampton, W. B. Sherman and A. Stull. J. A. M. A. *114:* 1854, 1940.

Elimination of Horse Serum Specificity from Antitoxins. R. D. Coghill, N. Fell, M. Creighton and G. Brown. J. Immunol. *39:* 207, 1940.

Physical Allergy. W. W. Duke. J. A. M. A. *84:* 736, 1925.

Allergy in Drug Idiosyncrasy. R. A. Cooke. J. A. M. A. *73: 759, 1919.*

COURSE NO. 3—SPECIAL MEDICINE
(November 8–19, 1943)

PHILADELPHIA INSTITUTIONS

CHARLES L. BROWN, M.D., F.A.C.P., *Director*

Fee, $40.00

The Advisory Committee on Postgraduate Courses of the College, in coöperation with authorities in Philadelphia and under the direction of Dr. Charles L. Brown, Professor of Medicine at Temple University School of Medicine, has drawn up an unique program, which should attract the interest of a large number of members of the College, as well as Medical Officers of the Armed Forces. It offers a short, but detailed, resumé in several different specialties. The plan is to allot approximately one-half day to the consideration of each of the special fields of medicine covered in the program. In most instances discussions will be conducted by authorities of national repute.

The concluding day, Friday, November 19, will be devoted to a Regional Meeting of the American College of Physicians for Pennsylvania, New Jersey, Delaware and adjacent territory. The program will consist of a series of clinics in the morning by the staff of the Hospital of the University of Pennsylvania; a luncheon at 1:00 P.M. at the College Headquarters, 4200 Pine Street; and an afternoon program, consisting of six important papers, three by Officers of the Armed Forces and three by outstanding civilian clinicians. In the evening there will be cocktails and dinner at the Benjamin Franklin Hotel, and an interesting program, in which Officers and Regents of the College and high ranking Officers of the Medical Corps of the Armed Forces will participate.

The following outline of the course is in some instances incomplete, or subject to minor changes.

OFFICERS OF INSTRUCTION (partial list only)

Edwin B. Abramson, M.D., Assistant, Medical Department, Jewish Hospital.

Kenneth E. Appel, M.D., F.A.C.P., Senior Psychiatrist, Institute of the Pennsylvania Hospital; Assistant Professor of Psychiatry, University of Pennsylvania School of Medicine.

Joseph T. Beardwood, Jr., M.D., F.A.C.P., Assistant Professor of Medicine, University of Pennsylvania Graduate School of Medicine.

Herman Beerman, M.D., Assistant Professor of Dermatology and Syphilology, School of Medicine and Graduate School of Medicine, and Assistant Director, Institute for the Control of Syphilis, University of Pennsylvania.

Mary A. Bennett, Ph.D., Physiological Chemist, Lankenau Hospital Research Institute.

Alton D. Blake, M.D., Resident in Pathology, Bryn Mawr Hospital.

Henry L. Bockus, M.D., F.A.C.P., Professor of Gastro-enterology, University of Pennsylvania Graduate School of Medicine.

Earl D. Bond, M.D., Director of Research, Institute of the Pennsylvania Hospital; Professor of Psychiatry and Vice Dean, University of Pennsylvania Graduate School of Medicine.

Robert W. Briggs, Ph.D., Biologist, Lankenau Hospital Research Institute.

Charles L. Brown, M.D., F.A.C.P., Professor of Medicine and Head of the Department of Medicine, Temple University School of Medicine.

W. Edward Chamberlain, M.D., F.A.C.P., Professor of Radiology, Temple University School of Medicine.

F. W. Chornock, M.D., Biochemist, Bryn Mawr Hospital.

Louis H. Clerf, M.D., F.A.C.P., Professor of Laryngology and Bronchoscopy, Jefferson Medical College of Philadelphia.

David A. Cooper, M.D., F.A.C.P., Physician to Division of Tuberculosis, Philadelphia General Hospital; Assistant Professor of Medicine, University of Pennsylvania School of Medicine and Graduate School of Medicine.

Gilbert L. Dunnahoo, M.D., Assistant Surgeon General, United States Public Health Service.

John Eiman, M.D., F.A.C.P., Assistant Professor of Pathology, University of Pennsylvania Graduate School of Medicine; Director of Laboratories, Abington Memorial Hospital.

Gilson C. Engel, M.D., Chief, Surgical Service "B," Lankenau Hospital; Assistant Professor of Surgery, University of Pennsylvania Graduate School of Medicine.

O. Spurgeon English, M.D., Professor of Psychiatry, Temple University School of Medicine.

A. F. Finkelstein, M.D., Associate in Radiology, University of Pennsylvania Graduate School of Medicine.

Harrison F. Flippin, M.D., F.A.C.P., Associate in Medicine, University of Pennsylvania School of Medicine and Graduate School of Medicine.

William I. Gefter, M.D., Clinical Instructor in Medicine, Woman's Medical College of Pennsylvania.

Horace R. Getz, M.D., Associate in Medicine, University of Pennsylvania School of Medicine.

Herbert M. Goddard, M.D., Coroner, City of Philadelphia.

Benjamin A. Gouley, M.D., Chief Coroner's Physician, City of Philadelphia.

George C. Griffith, M.D., F.A.C.P., Assistant Professor of Cardiology, University of Pennsylvania Graduate School of Medicine.

Joseph Hughes, M.D., Director of Laboratories, Institute of the Pennsylvania Hospital; Assistant Professor of Experimental Neurology, University of Pennsylvania Graduate School of Medicine.

Norman R. Ingraham, Jr., M.D., Chief, Division of Venereal Disease Control, Philadelphia Department of Public Health; Assistant Professor of Dermatology and Syphilology, School of Medicine, and Associate Director, Institute for the Control of Syphilis, University of Pennsylvania.

Rudolph Jaeger, M.D., Assistant Professor of Neurosurgery, Jefferson Medical College of Philadelphia.

Walter G. Karr, M.D., Assistant Professor of Biological Chemistry, University of Pennsylvania Graduate School of Medicine; Consultant Biochemist, Bryn Mawr Hospital.

Joseph V. Klauder, M.D., Associate Professor of Dermatology and Syphilology, University of Pennsylvania Graduate School of Medicine; Director, Ocular Syphilis Clinic, Wills Hospital.

William Harding Kneedler, M.D., Associate in Tropical Medicine, Jefferson Medical College of Philadelphia.

John A. Kolmer, M.D., F.A.C.P., Professor of Medicine, Temple University School of Medicine; Director, Research Institute of Cutaneous Medicine; Consultant in Serology, U. S. Public Health Service.

Karl Kornblum, M.D., Associate Professor of Radiology, University of Pennsylvania Graduate School of Medicine.

David W. Kramer, M.D., F.A.C.P., Assistant Professor of Medicine, Jefferson Medical College of Philadelphia.

Paul R. Leberman, Lt., (MC-V-S), U.S.N.R.

W. E. Lee, M.D., F.A.C.S., Vice Dean of Surgery, University of Pennsylvania Graduate School of Medicine.

Rubin M. Lewis, M.D., Acting Chief, Surgical Division, Tuberculosis, Philadelphia General Hospital; Clinical Associate Professor of Surgery, Woman's Medical College of Pennsylvania.

John S. Lockwood, M.D., F.A.C.S., Associate in Surgery, University of Pennsylvania School of Medicine.

Max B. Lurie, M.D., Assistant Professor of Experimental Pathology, University of Pennsylvania Graduate School of Medicine.

C. H. Mann, M.D., Research Institute, E. R. Squibb & Sons, New York, N. Y.

Albert G. Martin, M.D., Surgical Service "A," Lankenau Hospital; Assistant Instructor in Surgery, University of Pennsylvania Graduate School of Medicine.

Hans May, M.D., F.A.C.S., Surgical Service "B," Lankenau Hospital; Associate in Surgical Pathology, University of Pennsylvania Graduate School of Medicine.

Grace Medes, Ph.D., Physiological Chemist, Lankenau Hospital Research Institute.

Merle M. Miller, M.D., F.A.C.P., Associate in Allergy, University of Pennsylvania Graduate School of Medicine; Chief of Allergy Clinic, Graduate Hospital of the University of Pennsylvania.

J. Monaghan, M.D., Instructor in Gastro-enterology, University of Pennsylvania Graduate School of Medicine.

John R. Moore, M.D., F.A.C.S., Professor of Orthopedics, Temple University School of Medicine.

Julia Morgan, M.D., Professor of Tropical Medicine, University of Pennsylvania School of Medicine.

Harry E. Morton, Sc.D., Associate Professor of Bacteriology, University of Pennsylvania School of Medicine.

Meyer Naide, M.D., Instructor in Medicine, University of Pennsylvania School of Medicine.

H. Ostrum, M.D., Associate Professor of Radiology, University of Pennsylvania Graduate School of Medicine.

Harold D. Palmer, M.D., F.A.C.P., Senior Psychiatrist, Institute of the Pennsylvania Hospital; Professor of Psychiatry, Woman's Medical College of Pennsylvania.

Eugene Pendergrass, M.D., Professor of Radiology, University of Pennsylvania School of Medicine.

Wm. Harvey Perkins, M.D., F.A.C.P., Dean and Professor of Preventive Medicine, Jefferson Medical College of Philadelphia.

Alison H. Price, M.D., Fellow in Medicine, Jefferson Medical College of Philadelphia.

Hobart A. Reimann, M.D., Magee Professor of Practice of Medicine and Clinical Medicine, Jefferson Medical College of Philadelphia.

Stanley P. Reimann, M.D., F.A.C.P., Associate Professor of Surgical Pathology, University of Pennsylvania Graduate School of Medicine; Pathologist and Director of Research Institute, Lankenau Hospital.

John C. Reinhold, Ph.D., Principal Biochemist, Philadelphia General Hospital.

Jane Royle, M.A., Assistant Biologist, Lankenau Hospital Research Institute.

William G. Sawitz, M.D., Assistant Professor of Parasitology, Jefferson Medical College of Philadelphia.

Michael Scott, M.D., F.A.C.S., Assistant Professor of Neurosurgery, Temple University School of Medicine.

Florence Seibert, M.D., Associate Professor of Biochemistry, University of Pennsylvania School of Medicine.

Thomas A. Shallow, M.D., F.A.C.S., Professor of Surgery, Jefferson Medical College of Philadelphia.

Lauren H. Smith, M.D., F.A.C.P., Physician-in-Chief and Administrator, Institute of the Pennsylvania Hospital; Associate Psychiatrist, University of Pennsylvania School of Medicine.

Will Cook Spain, M.D., F.A.C.P., Professor of Clinical Medicine, New York Post-Graduate Medical School and Hospital, Columbia University; Chief of Allergy Clinic, New York Post-Graduate Medical School and Hospital; New York, N. Y.

John H. Stokes, M.D., Professor of Dermatology and Syphilology, School of Medicine and Graduate School of Medicine, and Director, Institute for the Control of Syphilis, University of Pennsylvania.

Edward A. Strecker, M.D., F.A.C.P., Consultant-in-Chief, Institute of the Pennsylvania Hospital; Professor of Psychiatry, University of Pennsylvania School of Medicine.

William D. Stroud, M.D., F.A.C.P., Professor of Cardiology, University of Pennsylvania Graduate School of Medicine; Cardiologist, Pennsylvania Hospital; Cardiologist and Director of the Heart Station, Bryn Mawr Hospital; Physician-in-Chief, Cardiovascular Service, Abington Memorial Hospital.

Max M. Strumia, M.D., Director of Laboratory of Clinical Pathology, Bryn Mawr Hospital; Assistant Professor of Pathology, University of Pennsylvania Graduate School of Medicine.

James M. Surver, M.D., F.A.C.S., Associate in Surgery, Jefferson Medical College of Philadelphia.

Charles Swalm, M.D., Assistant Coroner's Physician, City of Philadelphia.

Paul Swenson, M.D., Professor of Radiology, Jefferson Medical College of Philadelphia.

Gerrit Toennies, Ph.D., Organic Chemist, Lankenau Hospital Research Institute.

Louis N. Tuft, M.D., Assistant Professor of Medicine and Chief of Allergy Clinic, Temple University School of Medicine.

Henry Tumen, M.D., Assistant Professor of Medicine, University of Pennsylvania Graduate School of Medicine.

J. Vastine, M.D., Professor of Radiology, Woman's Medical College of Pennsylvania.

Matthew Walzer, M.D., Chief of Allergy Clinic, Jewish Hospital, Brooklyn, N. Y.

Edward Weiss, M.D., F.A.C.P., Professor of Clinical Medicine, Temple University School of Medicine.

William White, M.D., Research Fellow in Surgery, University of Pennsylvania School of Medicine.

Bernard P. Widmann, M.D., Professor of Radiology, University of Pennsylvania Graduate School of Medicine.

George Willauer, M.D., F.A.C.S., Associate in Surgery, Jefferson Medical College of Philadelphia.

Elizabeth Wilson, M.D., Assistant Coroner's Physician, City of Philadelphia.

Carroll S. Wright, M.D., Professor of Dermatology and Syphilology, Temple University School of Medicine; Associate Professor of Dermatology and Syphilology, University of Pennsylvania Graduate School of Medicine.

Thomas H. Wright, M.D., Clinical Director, Department for Mental and Nervous Diseases, Pennsylvania Hospital; Instructor in Psychiatry, University of Pennsylvania School of Medicine.

Joseph Yaskin, M.D., Professor of Neurology, University of Pennsylvania Graduate School of Medicine.

OUTLINE OF COURSE

Monday, November 8.

Psychosomatic Medicine

EDWARD WEISS, M.D., F.A.C.P., In Charge

TEMPLE UNIVERSITY SCHOOL OF MEDICINE

3400 N. Broad St.

X-Ray Museum, Sixth Floor

A.M.

9:00–11:00   Psychosomatic Conference.
              Cardiac Neurosis (Neurocirculatory Asthenia); Hypertension. Functional Indigestion; Cardiospasm; and Peptic Ulcer.
              Dr. Weiss and Dr. English.

11:00–12:00   Low Back Pain; Panel Discussion.
              Dr. Chamberlain, Dr. Moore, Dr. Scott and Dr. Weiss.

Monday, November 8.

Allergy

MERLE M. MILLER, M.D., F.A.C.P., In Charge

GRADUATE HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

19th and Lombard Sts.

North Lecture Room

P.M.

2:00– 2:20   Principles of Allergy.   Physiological Pathology of the Allergic State.
              Dr. Tuft.

2:20– 3:10   Seasonal Pollinosis.   Treatment of Hay Fever—Evaluation of Different Methods.
              Dr. Spain.

3:10– 4:00	Gastrointestinal Allergy. Experimental Alimentary Allergy. Clinical Evaluation. (Motion Pictures.) Dr. Walzer.
4:00– 4:20	Bronchial Asthma. Pathology. Dr. Eiman.
4:20– 5:00	Diagnosis and Treatment. Demonstration of Skin Testing. Passive Transfer. Dr. Miller.

Tuesday, November 9.

Syphilis
NORMAN R. INGRAHAM, JR., M.D., In Charge
HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA
34th and Spruce Sts.

A.M.

9:00– 9:10	Introductory Remarks: The Public Health Importance of Syphilis in War Times. Dr. Ingraham.
9:10– 9:50	The Problem of Falsely Positive Reactions in the Serology of Syphilis (Lecture and Discussion). Dr. Kolmer.
9:50–10:30	Blindness Caused by Syphilis (Lantern Slides, Illustrative Case Records and Charts). Dr. Klauder.
10:30–11:25	Standard Versus Intensive Treatment of Syphilis: Military and Civilian Applications (Lecture and Discussion). Dr. Stokes and Dr. Beerman.
11:25–12:00	Treatment Reactions to Antisyphilitic Therapy. Dr. Wright.

Tuesday, November 9.

Blood Diseases
MAX M. STRUMIA, M.D., In Charge
BRYN MAWR HOSPITAL
Bryn Mawr, Pa.
Assembly Room, Third Floor

P.M.

2:00– 3:00	The Hemolytic Diseases. Dr. Strumia.
3:00– 4:00	The Metabolism of Hemoglobin. Dr. Karr.
4:00– 5:00	Reticuloendotheliosis. Dr. Strumia.

Dr. Blake and Dr. Chornock will assist in the discussion and demonstration.

Wednesday, November 10.

Cardiovascular Diseases
WILLIAM D. STROUD, M.D., F.A.C.P., In Charge
PENNSYLVANIA HOSPITAL
8th and Spruce Sts.
(Detailed outline yet to come)

A.M.
9:00–12:00

Wednesday, November 10.

Peripheral Vascular Disorders

DAVID W. KRAMER, M.D., F.A.C.P., In Charge

JEFFERSON MEDICAL COLLEGE

1025 Walnut St.

Society Room

P.M.
2:00– 2:15	Evaluation of Various Methods of Investigating Peripheral Circulation. Dr. Kramer.
2:15– 2:30	Fluorescein as a Means of Investigating the Status of Peripheral Circulation. Dr. Abramson.
2:30– 2:45	Periarteritis Nodosa; Allergic Influences. Dr. Hobart A. Reimann and Dr. Price.
2:45– 3:00	Endarteritis Obliterans. Dr. Kramer.
3:00– 3:15	Phlebitis—Acute and Chronic; Treatment. Dr. Willauer.
3:15– 3:30	Freezing Therapy and Anesthesia for Gangrene. Dr. Surver.
3:30– 3:45	Amputation for Gangrene: When, Where and How? Dr. Shallow.
3:45– 4:00	Ganglionectomy for Peripheral Vascular Disorders: Indications and Choice of Procedure. Dr. Jaeger.
4:00– 4:15	Blood and Plasma in Treatment of Chronic Leg Ulcers. Dr. Naide.
4:15– 5:00	Evaluation of the Various Newer Methods in Treatment of Peripheral Vascular Disorders. Dr. Kramer.

Thursday, November 11.

Arthritis and Related Conditions

RALPH PEMBERTON, M.D., F.A.C.P., In Charge

ABINGTON MEMORIAL HOSPITAL

Abington, Pa.

A.M.
9:00–12:00

SYMPOSIUM

1. Statistical Factors.
2. Pathology.
3. Physiologic Disturbances Involved.
4. Clinical Presentation of Cases, with Emphasis on Diagnostic Methods and Treatment.
5. Round Table Discussion.
    Dr. Pemberton, Dr. Bach and Dr. Scull.

Thursday, November 11.

Gonorrhea

PAUL R. LEBERMAN, LT., (MC-V-S), U.S.N.R., and HARRY E. MORTON, SC.D.

U. S. NAVAL HOSPITAL

16th St. and Pattison Ave.

- Barracks A

P.M.

2:00– 5:00 Introduction.

Applied Anatomy and Histology of Lower Urinary Tract.
Gonococcus—Pathology of Gonorrhea.
Influence of Anatomic Structures.
Clinical Course of Gonorrhea.
Dr. Leberman.

Neisseria Gonorrheae.

Morphology of the Gonococcus.
Staining Reactions.
Biology of the Gonococcus (Susceptibility to temperature above body temperature. Relation to fever therapy).
Susceptibility to Temperatures below Body Temperature.
Precautions to Be Taken for Preservation of Specimens from Time of Collection until Cultured.
Susceptibility to Weak Alkali (Microscopic and macroscopic tests).
Susceptibility to Disinfectant Action of Chemicals.
Importance of 10% CO_2 and Moisture for Maximum Growth.
Cultivation.

Media Used for Satisfactory Growth of the Gonococcus.
Methods for Cultivating under 10% CO_2.
Comparison of the Efficiency of Culturing versus Smear Technique for Detecting the Gonococcus.
Morphology of Gonococcus Colonies.
Biochemical Reactions.

Oxidase Test.
Fermentation Tests.
Pathogenicity for Man and Other Animals.
Dr. Morton.

Diagnosis of Gonorrhea.

Technique of Gram Stain.
Technique of Culture Procedures.
Two Glass Test.
Considerations of Non-Gonorrheal Urethral Discharges.
Cause of Local Symptoms.
Dr. Leberman.

Treatment.

Local Medication.
Chemotherapy.
Tests of Cure.
Complications and Treatment Thereof.
General Principles and Application of Artificial Hyperpyrexia (Kettering Hypertherm Cabinet).
Dr. Leberman.

Management of Venereal Diseases in the Tropics.
Lymphopathia Venereum.
Dr. Mann.

Prevention and Control of Gonorrhea.
Prophylaxis.
Instruction to Patient.
Coöperating Agencies for Control.
1. LaFollette-Bulwinker Bill for the Control of Venereal Disease.
2. Mann Act.
3. May Bill.
Dr. Leberman.

Round Table Discussion.
Dr. Leberman.

Friday, November 12.

Respiratory Diseases

HOBART A. REIMANN, M.D., and LOUIS H. CLERF, M.D., F.A.C.P., In Charge

JEFFERSON HOSPITAL

10th and Walnut Sts.

Clinical Amphitheater

A.M.
9:00–10:30   Acute Diseases of the Upper and Lower Respiratory Tract.
Dr. Reimann.
10:30–12:00   Chronic Diseases of the Respiratory Tract.
Dr. Clerf.

Friday, November 12.

Tuberculosis

DAVID A. COOPER, M.D., F.A.C.P., In Charge

PHILADELPHIA GENERAL HOSPITAL

34th St. below Spruce St.

Lecture Room, First Floor, Tuberculosis Division

P.M.
2:00– 5:00   Tuberculin as a Tool in Tuberculosis Control.
Dr. Seibert.
Nutrition in Tuberculosis.
Dr. Getz.
Natural Resistance to Tuberculosis.
Dr. Lurie.
Surgery in Tuberculosis.
Dr. Lewis.
Clinical Conference.
Dr. Cooper and Staff.

Saturday, November 13.

Gastrointestinal Diseases

HENRY L. BOCKUS, M.D., F.A.C.P., In Charge

GRADUATE HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

19th and Lombard Sts.

North Lecture Room

A.M.

9:00–10:00   SECONDARY GASTROINTESTINAL DISORDERS
Gastrointestinal Reactions in Depression.
    Dr. Yaskin.
Abdominal Symptoms in Diabetes.
    Dr. Beardwood.
Gastrointestinal Allergy.
    Dr. Miller.

10:00–11:00   ROUND TABLE CONFERENCE—Dr. Bockus, Leader.
The Clinical Application of Liver Function Tests in:
    1. Jaundice.
       Dr. Tumen.
    2. Cirrhosis of the Liver.
       Dr. Monaghan.
    3. Cardiac Disorders.
       Dr. Griffith.

11:00–12:00   GASTRO-ENTEROLOGIC CONFERENCE: Case Problems.
Medical Aspects.
    Dr. Bockus.
Roentgenologic Aspects.
    Dr. Finkelstein.
Surgical Aspects.
    Dr. Lee.

Monday, November 15.

Chemotherapy

HARRISON F. FLIPPIN, M.D., F.A.C.P., In Charge

PHILADELPHIA GENERAL HOSPITAL

34th St. below Spruce St.

Surgical Amphitheater

A.M.

9:00–12:00   PANEL DISCUSSION: Chemotherapy.
Sulfamerazine and Sulfamethazine; Introductory Remarks.
    Dr. Flippin.
Sulfamerazine vs. Sulfadiazine—Clinical Evaluation.
    Dr. Gefter.
Sulfonamides—Pharmacology.
    Dr. Reinhold.
Sulfonamides and Penicillin—Laboratory Studies.
    Dr. Lockwood.
Penicillin—Clinical Evaluation.
    Dr. White.

Monday, November 15.

Diagnostic Roentgenology

BERNARD P. WIDMANN, M.D., In Charge

HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

34th and Spruce Sts.

X-Ray Lecture Room, Fourth Floor

P.M.
2:00– 5:00   Roentgenologic Problems in Diseases of the Chest.
    Dr. Kornblum.
Roentgenologic Consideration of Non-Surgical Lesions of the Breast.
    Dr. Vastine.
Roentgenologic Aspects of:
    (a) Platybasia.
    (b) Low Back Pain.
    Dr. Chamberlain.
Roentgenologic Problems in Bone Disease.
    Dr. Swenson.
Roentgenology of the Urinary Tract.
    Dr. Pendergrass.
Roentgenology of the Heart.
    Dr. Ostrum.
Roentgenologic Problems in Diseases of the Gastrointestinal Tract.
    Dr. Widmann.

Tuesday, November 16.

Psychiatry

LAUREN H. SMITH, M.D., F.A.C.P., In Charge

THE INSTITUTE OF THE PENNSYLVANIA HOSPITAL

111 N. 49th St.

Auditorium

A.M.
9:00–12:00   The Wish to Fall Ill (Case Seminar).
    Dr. Bond.
The Fundamentals of Clinical Psychiatry in the Community.
    Dr. Strecker.
The Use of the Electroencephalogram as a Diagnostic Aid.
    Dr. Hughes.
The Use of Physiological Adjuncts in Therapy.
    Dr. Palmer.
The Status of Shock Therapy.
    Dr. Smith and Dr. Wright.
The Use of the Psychotherapeutic Interview in General Medicine.
    Dr. Appel.

Tuesday, November 16.

Metabolic Problems

JOSEPH T. BEARDWOOD, JR., M.D., F.A.C.P., In Charge

GRADUATE HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

19th and Lombard Sts.

(Detailed outline yet to come)

P.M.
2:00– 5:00

Wednesday, November 17.

Tropical Medicine

WM. HARVEY PERKINS, M.D., F.A.C.P., In Charge

JEFFERSON MEDICAL COLLEGE

1025 Walnut St.

Auditorium

A.M.
9:00–12:00   Tropical Diseases of Potential Danger to This Country.
               Dr. Perkins.
               National and International Defenses against Tropical Diseases.
               Dr. Dunnahoo.
               Immunization in Tropical Diseases.
               Dr. Kneedler.
P.M.
2:00– 5:00   Diagnosis of Important Tropical Diseases.
               Dr. Sawitz and Staff; Dr. Morgan and Staff.

To be followed by laboratory demonstrations and discussion.

Thursday, November 18.

Tumors

STANLEY P. REIMANN, M.D., F.A.C.P., In Charge

THE LANKENAU HOSPITAL

Girard and Corinthian Avenues

Doctors' Library

A.M.
9:00–12:00   1. Carcinoma of the Stomach.
                  Dr. Engel.
               2. Problems of Transplantation of Normal and Tumor Tissue.
                  Dr. Briggs.
               3. Principles of Reconstruction after Removal of Tumors.
                  Dr. May.
               4. Carcinoma of the Rectum.
                  Dr. Martin.
               5. Sulfur Compounds and Growth.
                  Dr. Toennies, Dr. Medes and Dr. Bennett.
               6. A Few Growth Problems Solvable by Tissue Culture.
                  Dr. Royle.

Thursday, November 18.

Legal Medicine

HERBERT M. GODDARD, M.D., In Charge

PHILADELPHIA CITY MORGUE

13th and Wood Sts.

P.M.

2:00– 3:00 Cardiac Traumatism, Industrial and Accidental.
a. The usual types of cardiac traumatism seen in industry.
b. The relationship of coronary artery disease and trauma.
Dr. Gouley.

3:00– 3:30 Sudden Death Due to Hemorrhagic Necrosis of the Adrenal Glands
Associated with Meningococcic Infection.
Dr. Wilson.

3:30– 4:30 Demonstration of Fresh Pathologic Material from Cases of Sudden
Death.
Dr. Swalm, Dr. Wilson and Dr. Gouley.

Friday, November 19.

REGIONAL MEETING

OF THE

AMERICAN COLLEGE OF PHYSICIANS

A.M.

9:30–12:00 Medical Clinics.
Hospital of the University of Pennsylvania, O. H. Perry
Pepper, M.D., F.A.C.P., In Charge.

P.M.

1:00 Buffet Luncheon.
College Headquarters.

2:00– 5:00 General Session.
Papers by eminent authorities, both Service and Civilian.
(Detailed program later; also announcement of place of
meeting.)

6:30 Cocktail Party and Dinner-Meeting.
Benjamin Franklin Hotel.

ANNALS OF INTERNAL MEDICINE

PHYSIOLOGICAL REACTIONS OF THE THYROID STIMULATING HORMONE OF THE PITUITARY. II. THE EFFECT OF NORMAL AND PATHOLOGICAL HUMAN THYROID TISSUES ON THE ACTIVITY OF THE THYROID STIMULATING HORMONE *

By Rulon W. Rawson,† Ruth M. Graham, and Charlotte B. Riddell, *Boston, Massachusetts*

INTRODUCTION

Many investigators [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13] have demonstrated an impressive similarity between changes induced in laboratory animals treated with the thyroid stimulating hormone of the pituitary (TSH), and the clinical entity, Graves' disease. Such changes include hyperplasia of the thyroid, tachycardia, weight loss, increase in oxygen consumption, and exophthalmos. On the basis of such observations one might be tempted to conclude that the pituitary is a factor in the etiology of clinical thyrotoxicosis. However, one serious objection to such a conclusion is the fact that several investigators [14, 15, 16, 17, 18] have failed to demonstrate the thyrotropic hormone in the urine of thyrotoxic patients. Hertz and Oastler [14] found a thyroid stimulating substance in the urine of nine myxedematous patients, but were unable to demonstrate any thyrotropic effect in the urine of normal or thyrotoxic individuals. Rawson and Starr [16] found demonstrable amounts of thyrotropic substances in the urine of normal medical students. They found a strongly positive thyroid stimulating effect in the urine of three men who had had total thyroidectomies, and in the urine of a majority of non-myxedematous patients whose basal metabolic rates varied between −34 and −17. How-

ever, there was no evidence of a thyroid stimulating substance in the urine of 12 out of 14 thyrotoxic patients studied by these investigators.

In the light of the above observations it has been suggested [10, 20, 21] that there exists a balance between the thyroid and the pituitary, and that any deficiency in the thyroid stimulates the pituitary to produce more of the thyroid stimulating hormone, and conversely, supplying the thyroid hormone reduces the anterior pituitary secretion of TSH. Salter [22] has called this the pituitary thyroid axis. On the basis of this theory one might explain the absence of any demonstrable TSH in the urine of thyrotoxic patients as being due to a suppression of the pituitary by an increased secretion of thyroid hormone. Another interpretation [12] has been suggested based on work reported by Loeser,[23] namely that the absence of thyrotropic substances from the body fluids of hyperthyroid patients might be due to an alteration or retention of the TSH by the overactive thyroid. Loeser injected 3000 units of TSH into intact rabbits and recovered the hormone from the blood for only one hour. However, he was able to demonstrate the hormone in the circulating blood of thyroidectomized rabbits treated in a similar manner for seven hours. Similarly Seidlin [24] recovered the hormone from the urine of thyroidectomized guinea pigs previously treated with large doses of TSH, but he was unable to demonstrate any thyrotropic activity in the urine of intact guinea pigs treated in a similar fashion.

In a previous publication [25] we reported that the thyroid stimulating hormone after being exposed by means of tissue culture technics to explanted adult rabbit thyroid tissues had lost its characteristic thyroid stimulating activity. Exposure to control tissues, except thymus and lymph nodes, did not diminish the activity of the thyroid stimulating hormone. We suggested that such findings might explain the reported absence of thyroid stimulating substances from the urine of patients with the thyrotoxicosis of Graves' disease.

The purpose of the present investigation has been to determine by means of tissue culture technics whether there is any difference in the effect of various types of human thyroid tissue on the activity of the thyroid stimulating hormone.

Methods. Human thyroids * removed at operation were used in this study. The toxic goiters were removed after the patients had received the usual preoperative treatment with rest and iodine. Small amounts of normal human thyroid tissue were obtained for this study by Dr. Oliver Cope at operations for parathyroid tumors. The non-toxic nodular thyroid tissue was obtained from routine operations for such goiters. For each experiment thyroid tissue weighing approximately 150 mg. was sliced and explanted in roller bottles [26] which had been coated with chicken plasma. A bathing fluid consisting of 15 c.c. of Tyrode's [27] solution, which contained the thyroid

stimulating hormone † in a concentration of one-half Junkmann-Schoeller [28] guinea pig unit per c.c. was added to each explant. The bottles were rotated 15 revolutions per hour in an incubator at 38° C. for 24 hours. Following such an exposure the medium was withdrawn and assayed for thyroid stimulating effect, in duplicate, on two one day old chicks, according to the micro-histometric technic described by Starr and Rawson [29, 16] and by Rawson and Salter.[30] Two one day old chicks were each injected with one c.c. daily of the test medium for three days, and were autopsied on the fourth day. The thyroids were removed immediately and fixed in 10 per cent neutral formalin for 24 hours and then dehydrated in alcohol and embedded in paraffin. Sections were cut at 6 micra and stained with hematoxylin and eosin. Each section was examined under the oil immersion lens and inspected systematically from end to end in parallel pathways until 100 acini had been examined. Each acinus in the path of crossing which presented a definite wall, and was cut cross-sectionally, was included in the study. From each acinus one representative cell was chosen and its height determined by means of an ocular micrometer. Frequency curves were plotted from the observed measurements, and the mean acinar cell height of each examined thyroid was derived. To provide a standard measure of activity of the assayed media four groups of day old chicks were injected on three successive days with thyrotropic hormone in dilutions equivalent to ⅛, ¼, ½, and one unit. The mean acinar cell heights (MCH) of such test thyroids were determined as described above and compared with those of 10 control animals which had thyroid mean cell heights varying between 3.8 and 4.2 micra. The MCH of this group of thyroids averaged 4.0 micra. Four chicks treated with three daily injections of TSH in a concentration of ⅛ unit had thyroid mean cell heights which varied between 6.0 and 6.2 micra. The thyroid MCH of four chicks treated with ¼ unit daily for three days varied between 7.0 and 7.3 micra. These assays had an average MCH of 7.2 micra. Ten animals treated with ½ unit daily had thyroid mean cell heights which averaged 8.2 micra and varied between 7.8 and 8.3 micra. The average MCH of four animals treated with one unit daily was 9.0 micra and had a range between 8.8 and 9.2 micra (figure 1).

Results. Tissues from eight non-toxic nodular goiters were explanted and bathed in Tyrode's solution containing ½ unit of TSH per c.c. The basal metabolic rates of the donor patients before operation varied between minus 21 and minus 10. Assays of the bathing fluids showed no loss of thyrotropic activity. The mean cell heights of animals injected with media following exposure to these nodular goiters varied between 7.8 and 8.8 micra. The average MCH of this group of assay animals was 8.3 micra. Normal thyroid tissue from seven patients whose basal metabolic rates varied between minus 6 and plus 10 caused a loss of about one-half of the original thyrotropic activity in the bathing media which before exposure to these

normal thyroids contained TSH in a concentration equivalent to ½ unit per
c.c. The thyroid mean acinar cell height of 14 test animals treated with
such media varied between 6.3 and 7.2 micra and averaged 6.8 micra. These
thyroid mean cell heights are comparable to those of animals treated with
¼ unit of TSH daily in the standard response group studies.

Tissue from 20 thyroids removed from patients with Graves' disease
was explanted and exposed in each experiment to 15 c.c. of Tyrode's solution
containing TSH in a concentration equivalent to ½ unit per c.c. The period
of exposure was 24 hours. Assays of these exposed media demonstrated a
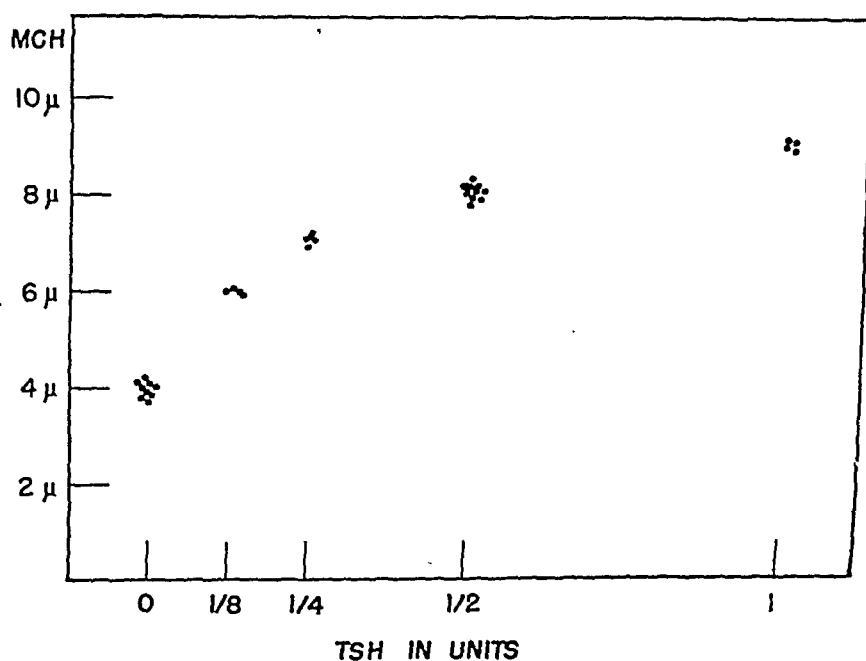
FIG. 1. Response of normal chick thyroid to increasing quantities of injected TSH.
The ordinate shows mean cell heights, MCH, in micra, the abscissa the dose of TSH in
Junkmann-Schoeller units.

loss of the major part of the TSH activity. The thyroid mean acinar cell
height of 40 assay animals treated with these media following exposure to
toxic thyroid tissue varied between 4.1 and 5.7 micra and averaged 4.5
micra.

Since it has been suggested that the apparent inactivation of the TSH
here observed might be due to the interference of the normal TSH action
on the test chicks' thyroids by some hormonal or metabolic substance washed
out of the thyroid tissue slices and into the bathing medium, the following
control studies were done. Two equal amounts of thyroid tissue from each
of nine thyrotoxic patients were explanted into separate bottles. The
medium added to one bottle contained TSH in a concentration equal to ½
unit per c.c. The medium in the corresponding bottle contained no pituitary
hormone. At the end of the 24 hour exposure, TSH in a concentration
equivalent to ½ unit per c.c. was added to the medium from the second

bottle, and both media were assayed in the usual manner. Assays of the media which contained the TSH during the period of exposure showed a loss of the normal TSH activity. When the hormone was added to the medium after exposure to the thyroid tissue slices there was no loss of TSH activity. The mean acinar cell heights of animals treated with the latter media averaged 8.1 micra (figure 2).

Two patients who presented clinical pictures of discrete toxic adenomata were seen during this period of study. Explants were made of the adenomatous processes as well as of the surrounding normal tissue, and the effect
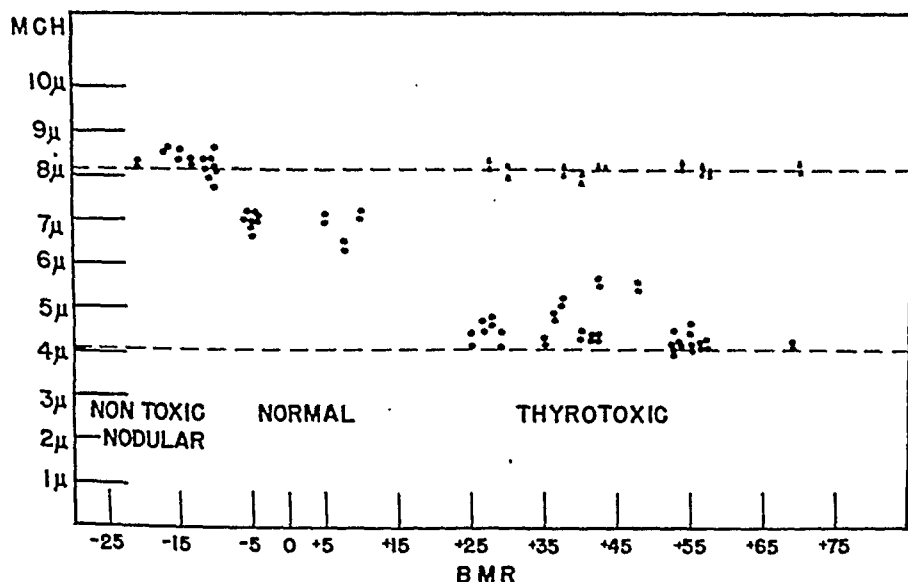
Fig. 2. Response of chick thyroid to injection of media containing TSH in the concentration of ½ Junkmann-Schoeller unit per c.c. after these had been exposed to human thyroid tissue (goiter) explants. Shown by dots. The ordinate discloses the mean cell heights, MCH, in micra, and the abscissa the BMR of the patient from whom the explanted material was derived. The left-hand flock of dots at the level of MCH 8 micra, and BMR — 21 to — 10, are for non-toxic nodular goiter cases. The next flock, MCH around 7 micra, and BMR — 6 to + 10, are for normal thyroids, and the right-hand flock, MCH from 4 to 5 micra, and BMR + 25 to + 65, are for toxic hyperplastic goiters. The black triangles show the thyroid MCH of chicks injected with TSH, ½ unit per c.c. which had been added to the medium only after the latter had been exposed to explants of toxic thyroid tissue. It is to be noted that no inactivation took place (see text). The lower horizontal broken line indicates the average thyroid MCH of ten untreated chicks; the upper, that of ten chicks treated with ½ unit of TSH.

of these tissues on the activity of the exposed thyroid stimulating hormone was determined.

One of these patients, Mrs. C., an Italian woman of 33, had noted an enlargement in the region of the left lobe of her thyroid seven years before, following a pelvic operation. This nodule increased in size gradually, but more rapidly in the three months just prior to admission. During the period of more rapid growth the patient noted some hoarseness and also some palpitation. She also complained of tremor of the hands. She had not noted any weight loss, but had had a marked increase in appetite. On

physical examination a 5 cm. rounded nodule in the upper portion of the left lobe of the thyroid was observed. This nodule was firm and non-tender. The hands were warm and tremulous when extended. The basal metabolic rate (BMR) was plus 24. Following two weeks on iodine there was no change in the BMR. At operation the thyroid adenoma, which after removal weighed 19 grams, was quite vascular and was removed completely. The right lobe was found to be pale and atrophic. A piece of the right lobe was removed for histologic examination and for in vitro studies. Eight days following the removal of the adenoma the BMR was minus one. The pulse rate which had been in the neighborhood of 100 to 120 fell to 70. Symptoms of palpitation disappeared and the patient admitted to being less nervous than before the operation. The adenomatous tissue when exposed to TSH containing medium, in tissue culture bottles, exerted an inactivating effect on the pituitary hormone. The apparently atrophic tissue found on the opposite side of the thyroid failed to inactivate any of the exposed TSH. The thyroid mean acinar cell heights of animals treated with media following exposure to the adenomatous and the atrophic tissue were 4.7 and 4.8 micra, and 8.0 and 8.5 micra respectively.

The second patient presenting a picture of toxic adenoma was a 23 year old white American born woman who entered the hospital complaining of nervousness and weakness. She had an intolerance to heat, and reported an increasing appetite with no loss of weight. She also complained of dyspnea and palpitation. On physical examination she was found to have a diffusely enlarged thyroid that did not transmit a bruit. She had prominence of the eyes with some lid lag, and was found to have a rapid and bounding pulse. Her basal metabolic rate was plus 24. She was instructed to take potassium iodide and was discharged on a medical régime. She did not make a good response to iodine. In the Out-patient Department her basal metabolic rates varied between plus 25 and plus 35. The left lobe of the thyroid gradually increased in size, and though the tissue on the right side of the trachea was palpable, it seemed definitely smaller and less involved than the tissue palpable on the left side. A left hemithyroidectomy was done and a biopsy was taken from the right lobe which at operation appeared to be normal except for two small nodules palpated deep in the central portion of the lobe near the trachea. Following the hemithyroidectomy the patient gained five kilograms in weight and had a marked improvement in symptoms. Her metabolic rate fell gradually to plus 2. Equal amounts of tissue from the removed adenoma and from the biopsied, apparently normal thyroid tissue, were explanted and exposed in parallel experiments to bathing media containing ½ unit of TSH per c.c. for 24 hours. Thyroid mean acinar cell heights of test animals treated with medium after its exposure to the adenomatous tissue were found to be 4.1 and 4.3 micra indicating an almost complete inactivation of TSH. Media following exposure to the apparently normal tissue contained about one-half of the original TSH activity, thus in-

activating about the same amount of TSH as normal thyroids were observed to have done. The mean acinar cell heights of such assay thyroids were 7.1 and 7.1 micra.

DISCUSSION

These findings indicate that normal human thyroid tissue can inactivate its stimulator, the thyrotropic hormone, when the latter is exposed to the thyroid tissue in vitro. This inactivating effect of normal human thyroid tissue on TSH is similar to that observed in comparable in vitro studies on the effect of rabbit thyroid tissue on the activity of TSH. In terms of tissue weight, however, the normal human thyroid does not inactivate the same quantity of hormone as does the rabbit thyroid. This difference can probably be explained as a variance in species response. Dr. Ruth E. Cortell, working in our laboratory, has observed in studies on tissue respiration with Warburg technics that the oxygen consumption of thyroid tissue varies from one species to another. She has also observed that the human thyroid has a much lower rate of oxygen consumption than that of any animal thyroids studied.

The observation of variations in the amount of hormone inactivated by pathologic human thyroid tissue as compared to the amount of hormone altered by normal human thyroid tissue is probably of real significance in considering the pathologic physiology of thyroid disease. The observed failure of the non-toxic nodular thyroid tissue to inactivate its stimulator may provide an explanation for the low basal metabolic rates so frequently observed in many non-toxic goiterous patients. Conversely the observed increased ability of thyroid tissue removed from people suffering from Graves' disease to inactivate the thyroid stimulating hormone may point to an increased sensitivity of such diseased thyroid tissue to normal, or possibly increased amounts, of the pituitary secreted thyroid stimulator. On the basis of these observations one might advance the hypothesis that thyroid function is, at least in part, dependent upon the ability of the end organ to respond to its stimulator. The varying effects of normal and pathologic thyroids on the TSH may well direct our attention in endocrine research to studies of the end organs and their responses to various hormonal actions. It seems plausible that various endocrinopathies may be on the basis of abnormal responses of the end organs to hormonal actions as well as on the basis of abnormal amounts of secreted hormones. Indeed the varying effects observed of toxic adenomatous tissue and non-diseased tissue taken from the same thyroid glands, on the activity of the exposed TSH in parallel experiments, suggests that certain abnormal states may be dependent upon the reactivity of localized cellular groups. Lein[31] has reported observations that likewise indicate variations in the metabolism of various types of thyroid tissue. He reported that toxic thyroid tissue when subjected to oxygen consumption studies in the Warburg tissue respirometer had a greater QO_2 than

normal or non-toxic goiterous tissue. He also found that the latter tissue consumed oxygen at a slower rate than did normal tissue.

Since we have observed in this study that thyroid tissue removed from patients with thyrotoxicosis inactivates nearly twice as much TSH as does normal human thyroid tissue, it seems quite possible that the reason for our inability to demonstrate with present methods any thyroid stimulators in the urine of thyrotoxic patients might be due to the complete inactivation of the secreted TSH by the overactive thyroid.

To explain the reaction as described is difficult with our present limited knowledge of cellular physiology and chemistry. Since bathing media containing no pituitary hormone, after 24 hour exposures to tissue slices of toxic thyroids, did not inhibit the action of TSH added to the media following removal from the tissue cultures, it seems unlikely that the observed inactivation of the exposed thyrotropic hormone was on the basis of inhibition by thyroid hormonal substances washed out of the tissue slices. Another possible mechanism of such an inactivation of the hormone is that of an enzymatic oxidative reaction. Investigations are now in progress in our laboratory to determine whether such phenomena exist in the pituitary thyroid axis.

SUMMARY

1. Observations have been made on the effect of normal and pathologic human thyroid tissues upon the activity of pituitary thyroid-stimulating hormone exposed to them by means of tissue culture technics (explants).

2. It was observed that the thyroid stimulating effect of a pituitary extract is significantly diminished following its exposure to normal human thyroid tissue.

3. Non-toxic goiterous tissue explants were observed to exert no effect on the activity of the TSH exposed to them.

4. Tissue slices taken from thyroids of patients with Graves' disease were found to inactivate about twice as much TSH as equal amounts of normal human thyroid tissue.

5. The hypothesis is advanced that the observed absence of thyrotropic hormone from the urine of thyrotoxic patients is due to the complete inactivation of TSH by the overactive thyroid of Graves' disease.

6. It is suggested that investigations in endocrine physiology, both normal and morbid, should include consideration of the state of the end organs in interpreting hormonal responses.

BIBLIOGRAPHY

1. UHLENHUTH, E., and SCHWARTZBACH, S.: Anterior lobe substance, the thyroid stimulator. The effect of anterior lobe substance on the thyroid gland, Proc. Soc. Exper. Biol. and Med., 1928, xxvi, 152.

2. UHLENHUTH, E.: The thyreoactivator hormone. Its isolation from the anterior lobe of the bovine pituitary gland and its effects on the thyroid gland, Trans. Am. Assoc. for the Study of Goiter, 1936, page 25.

3. LOEB, L., and BASSETT, R. B.: Effect of hormones of anterior pituitary on thyroid gland in guinea pig, Proc. Soc. Exper. Biol. and Med., 1929, xxvi, 860.

4. LOEB, L., and FRIEDMAN, H.: Exophthalmos produced by injections of acid extract of anterior pituitary gland of cattle, Proc. Soc. Exper. Biol. and Med., 1932, xxix, 648.

5. SEIBERT, W. J., and SMITH, R. S.: Effect of various anterior pituitary preparations on basal metabolism in guinea pigs, Proc. Soc. Exper. Biol. and Med., 1930, xxvii, 622.

6. MARINE, D., and ROSEN, S. H.: Exophthalmos in thyroidectomized guinea pigs by thyrotropic substance of anterior pituitary and mechanism involved, Proc. Soc. Exper. Biol. and Med., 1933, xxx, 901.

7. FRIEDGOOD, H. B.: Experimental exophthalmos and hyperthyroidism in guinea pigs, Bull. Johns Hopkins Hosp., 1934, liv, 48.

8. ANDERSON, E. M., and COLLIP, J. B.: Studies on the physiology of thyrotropic hormone of anterior pituitary, Jr. Physiol., 1934, lxxxii, 11.

9. COLLIP, J. B.: Diabetogenic, thyrotropic, adrenotropic and parathyrotropic factors of the pituitary, Jr. Am. Med. Assoc., 1935, civ, 916.

10. COLLIP, J. B., and ANDERSON, E. M.: Studies on thyrotropic hormone of the anterior pituitary, Jr. Am. Med. Assoc., 1935, civ, 965.

11. SMELSER, G. K.: Comparative study of experimental and clinical exophthalmos, Am. Jr. Ophth., 1937, xx, 1189.

12. LAMBIE, C. G.: The thyreotrophic hormone and its relation to clinical syndromes, Med. Jr. Australia, 1939, ii, 819 and 853.

13. AIRD, R. B.: Experimental exophthalmos and associated myopathy induced by thyrotropic hormone, ANN. INT. MED., 1941, xv, 564.

14. HERTZ, S., and OASTLER, E. G.: Assay of blood and urine for thyrotropic hormone in thyreotoxicosis and myxedema, Endocrinology, 1936, xx, 520.

15. COPE, C. L.: The anterior pituitary lobe in Graves' disease and in myxedema, Quart. Jr. Med., 1938, vii, 151.

16. RAWSON, R. W., and STARR, P.: Direct measurement of height of thyroid epithelium. A method of assay of thyrotropic substance; clinical application, Arch. Int. Med., 1938, lxi, 726.

17. JONES, M. S.: Study of thyrotropic hormone in clinical states, Endocrinology, 1939, xxiv, 665.

18. ROBINSON, A. R.: Thyreotrophic and antithyreotrophic factors in some types of thyroid disease, Med. Jr. Australia, 1941, i, 349.

19. MARINE, D.: The pathogenesis and prevention of simple endemic goiter, Jr. Am. Med. Assoc., 1935, civ, 2334.

20. MEANS, J. H.: Diseases of the thyroid gland, New England Jr. Med., 1939, ccxxi, 820.

21. UOTILA, U. U.: Regulation of thyrotropic function of thyroxin after pituitary stalk section, Endocrinology, 1940, xxvi, 129.

22. SALTER, W. T.: Endocrine function of iodine, 1940, Harvard University Press, Cambridge.

23. LOESER, A.: Die schilddruesenwirksame Substanz des Hypophysenvorderlappens, Arch. f. exper. Path. u. Pharmakol., 1934, clxxvi, 697.

24. SEIDLIN, S. M.: Metabolism of thyrotropic and gonadotropic hormones, Endocrinology, 1940, xxvi, 696.

25. RAWSON, R. W., STERNE, G., and AUB, J. C.: Physiological reactions of thyroid stimulating hormone of the pituitary. I. Its inactivation by exposure to thyroid tissue in vitro, Endocrinology, 1942, xxx, 240.

26. SHAW, D. T., KINGSLAND, L. C., and BRUES, A. M.: Roller bottle tissue culture system, Science, 1940, xci, 148.

27. PARKER, R. C.: Methods of tissue culture, 1938, Paul B. Hoeber, Inc., New York.

28. JUNKMANN, K., and SCHOELLER, W.: Ueber das thyreotrope Hormon des Hypophysen-vorderlappens, Klin. Wchnschr., 1932, xi, 1176.

29. STARR, P., and RAWSON, R. W.: A graphic representation of thyroid response to stimulation by thyrotropic hormone, Proc. Soc. Exper. Biol. and Med., 1937, xxxv, 603.

30. RAWSON, R. W., and SALTER, W. T.: Microhistometric assay of thyrotropic hormone in day old chicks, Endocrinology, 1940, xxvii, 155.

31. LEIN, A.: Studies on the activity of the goitrous thyroid gland, Proc. Fed. Am. Soc. Exper. Biol., 1942, i, 50.

PERSONNEL SELECTION: A SHORT METHOD FOR SELECTION OF COMBAT OFFICERS *

By C. W. Heath, W. L. Woods, L. Brouha, C. C. Seltzer, and A. V. Bock, *Cambridge, Massachusetts*

For the past four years the Grant Study of the Hygiene Department at Harvard has been engaged in investigations concerning healthy, normal young men. In these investigations the technic of the fields of medicine, anthropology, physiology, social studies, psychology and psychiatry were employed, and the procedure by which the different technics were all applied to the same young men was essentially coöperative. Detailed information of wide scope was obtained on about 270 young college men who were unselected save for health and "normality." A simple system of classifying personality traits of normal persons was developed by which, to a certain degree, a diagnosis of the "normal" was attainable.

The classification of persons as "normal" does not need to be based only on the absence of disease. For example, one simple way of characterizing a "normal" person is by stating what he can do. Indeed, the original meaning of the word "person" is "the part which he must play." Moreover, there are no insurmountable difficulties in finding out what people can do, so that methods of exploring potentialities of people can be rather easily developed. This approach to the study of people avoids the usual method of searching for disease or potential disease, psychopathology or potential psychopathology, although such disabilities inevitably emerge from procedures of this nature.

In the past year this study has been focused particularly on aids in the selection of personnel for various occupations. It is our purpose to summarize, as an example, a short method for selection of combat officers to which most of our time recently has been devoted.[1] Variations of the method can be applied to the selection of non-combat officers and candidates for civilian trades. Emphasis has been placed on having a method as short as is consistent with reasonable accuracy and one which can be used in addition to present methods. It is assumed that preliminary medical examination, mental tests and other data have been obtained. Many details of a complete personality study have been eliminated.

A combat officer should be physically fit, have certain personality qualities for leadership and a physique which will give him presence and enable him to withstand hardship. This method combines these three qualities in three tests which are as follows:

(1) An eight minute test of physical fitness, which gives an accurate measure of the ability of the man to withstand hard muscular work and

enables him to be grouped as excellent, good, average or poor in physical fitness.

(2) A 10 minute interview devoted to the study of the personality and activities, which permits classification of the man as excellent, acceptable, doubtful or poor officer material.

(3) A brief inspection of the body build to determine characteristics of masculinity which have been found to be related to physical fitness and combat officer fitness.

The test for physical fitness has been applied to over 8,000 college students, large groups of Naval Aviation Cadets, a group of Commandos in England and many high-school boys and college girls. It has been introduced in the Navy and Army Aviation training programs. Initial studies with the short interview method were made on members of the Army R.O.T.C. for whom a rating based on at least two years' performance was available. There was good agreement, ranging from 93 to 100 per cent between the rating made by the short interview and that given by the Army officers. Subsequently, the test has been applied to other classes of the Army and Naval Reserve Officer Training Corps, candidates for the Army Enlisted Reserve Corps at Harvard College, and applicants for commissions at the Office of Naval Officer Procurement of the First Naval District. Well over 2,000 interviews have been performed. Estimates of body build have been made on many thousands of college students and others.

I. A Short Method of Estimating Physical Fitness: The Step Test. The test for estimating physical fitness has evolved out of many years of continued research by many workers at the Harvard Fatigue Laboratory. It is a simplification of more elaborate technics which have included measurements of heart rate, blood pressure, pulmonary ventilation, oxygen consumption, blood sugar and lactate variations in relation to degrees of work usually performed on a motor-driven treadmill. Many complicated technics can be eliminated for practical purposes and satisfactory estimation of a man's fitness for hard work can be made by exposing him to a simple standard form of exhausting exercise and taking into account two factors: the length of time the exercise can be sustained and the speed of recovery of the heart rate upon completion of the exercise. This simplification of method has been the result of recent work, particularly by R. E. Johnson, L. Brouha and R. C. Darling.[2, 3, 4]

The simplified test for physical fitness under consideration is called the "Step Test" and is performed as follows: the subject steps up and down a 20 inch platform 30 times a minute for five minutes or until he has to stop from exhaustion. An observer counts the time as in military marching as follows: "*Up*—2—3—4, *Up*—2—3—4," the "*up*" coming every two seconds. The subject then is seated and his pulse is counted from 1 to $1\frac{1}{2}$; 2 to $2\frac{1}{2}$, and 3 to $3\frac{1}{2}$ minutes after the exercise is discontinued. The score, or index of physical fitness is computed by dividing the duration of exercise

in seconds by twice the sum of half-minute pulses in recovery ($\times$ 100). As many men can take the test at one time as there are observers to count pulses.

The meaning of the figure thus obtained has been found in healthy young men to be as follows:

Below 55   = Poor physical condition
From 55 to 64 = Low average
From 65 to 79 = High average
From 80 to 89 = Good
Above 90   = Excellent

Figures 1 and 2 show the distribution of scores in college freshmen before and after conditioning and in a commando unit.
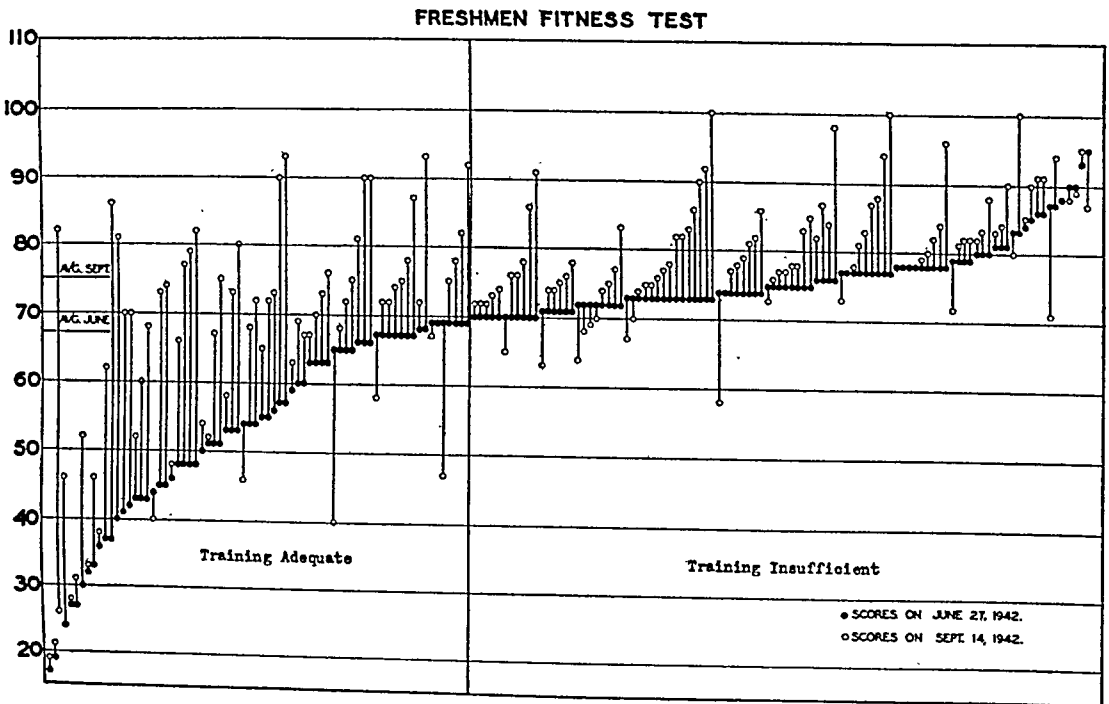
FIG. 1. The physical fitness index in a sample of the freshman class at Harvard. The black dots represent the scores for physical fitness on entrance before the course of physical training. The white dots are the scores of these men after 10 weeks of physical training. The average score before training of this group was 67; after training 75. The men less physically fit gained more than those more fit, showing that the training was not severe enough for the fit men. Those that scored less on the second trial had ill health or for some reason did not take the training. Varsity athletes in training score as a rule above 90. The best record was 180, made by the stroke of the Varsity crew.

This test measures general physical fitness independent of any particular strength or skill. It utilizes large muscle groups, places the cardiovascular and respiratory systems under definite stress and takes into account ability to recover from exertion. The scores have little relationship to those obtained with the Schneider, the McCloy, or the McCurdy-Larson tests which may be useful in detecting various failures of the cardiac and circulatory mechanisms, but are not always reliable for evaluating fitness for hard work

in healthy individuals. It is not necessary to take into account the pulse rate before the exercise because this has been found to have almost no relationship to physical fitness in healthy subjects.* The pulse rate at rest may be extraordinarily low in certain athletes who have been in training for years, but in general the pulse rate at rest is no indication of physical fitness in healthy young men. Emotional factors may increase greatly the pulse before exercise or before the medical examination, and this has been found to occur in both the physically fit and the physically unfit.[5]

When the test is applied to men who have been leading sedentary lives, it will probably not distinguish between those who will respond well to physi-
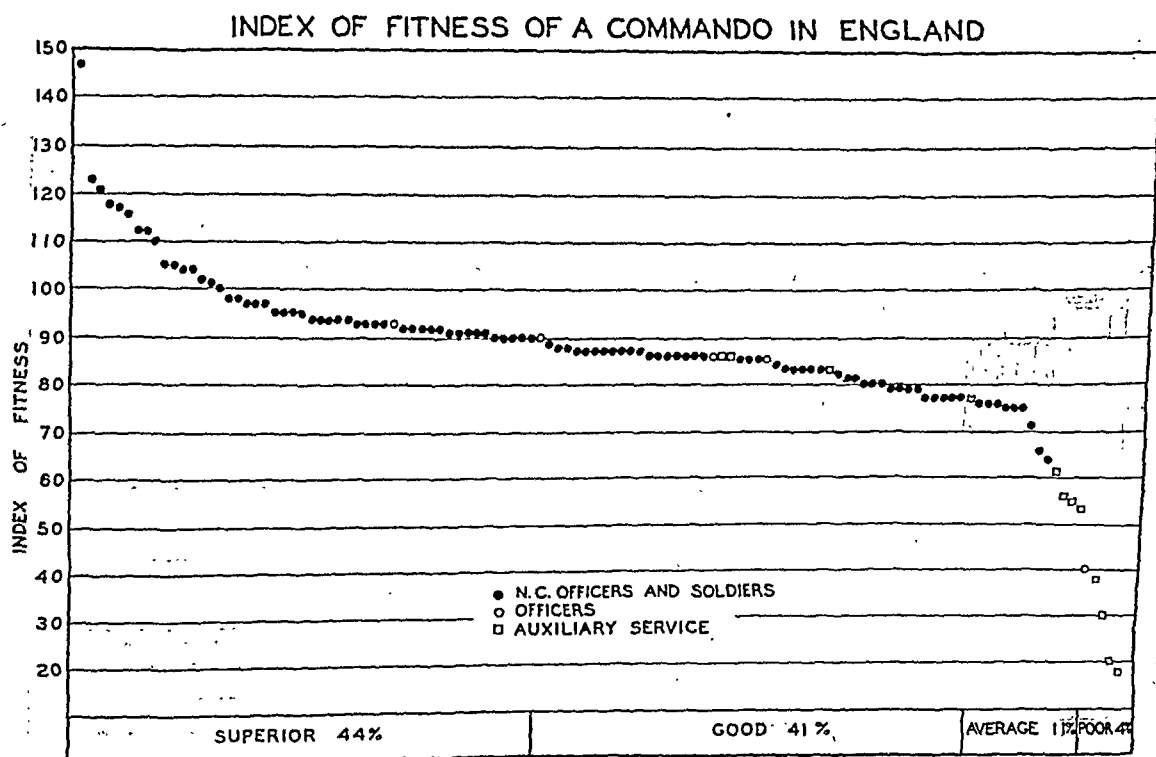
FIG. 2. The dots are the scores of individuals in a Commando unit in England. The average score was 90, which is comparable to that of Varsity athletes in training. The men with low scores should be eliminated from the group as they will hold back the better men.

cal training and those who will not. It will help to differentiate homogeneous groups of men for physical training or combat work, so that the progress of the whole group will not be held down to that of the poorest, and it will assist coaches and others having to do with the physical training of men.

II. A Short Interview for the Selection of Combat Officers. Dr. William Woods has been particularly responsible for the development of this short interview method for selection of combat officers. The approach is clinical and the task is to judge by personality traits whether a man is to be

---

* Data at hand, however, indicate that pulse rate taken under standard conditions may be related to personality traits and possibly to certain constitutional traits.

judged excellent or good (A), acceptable (B), questionable or doubtful (C), or poor (D) officer material. The time is limited to 10 minutes only. The examination is different from the ordinary psychiatric examination which attempts to weed out unsound individuals or those who betray manifestations of psychoneurosis, mood disorders, and intellectual inadequacy. The assumption is that such individuals have already been eliminated and that we are dealing with essentially healthy and normal young men. Nevertheless,

COMPARISON OF ATHLETIC ABILITY AND SHORT INTERVIEW RATING
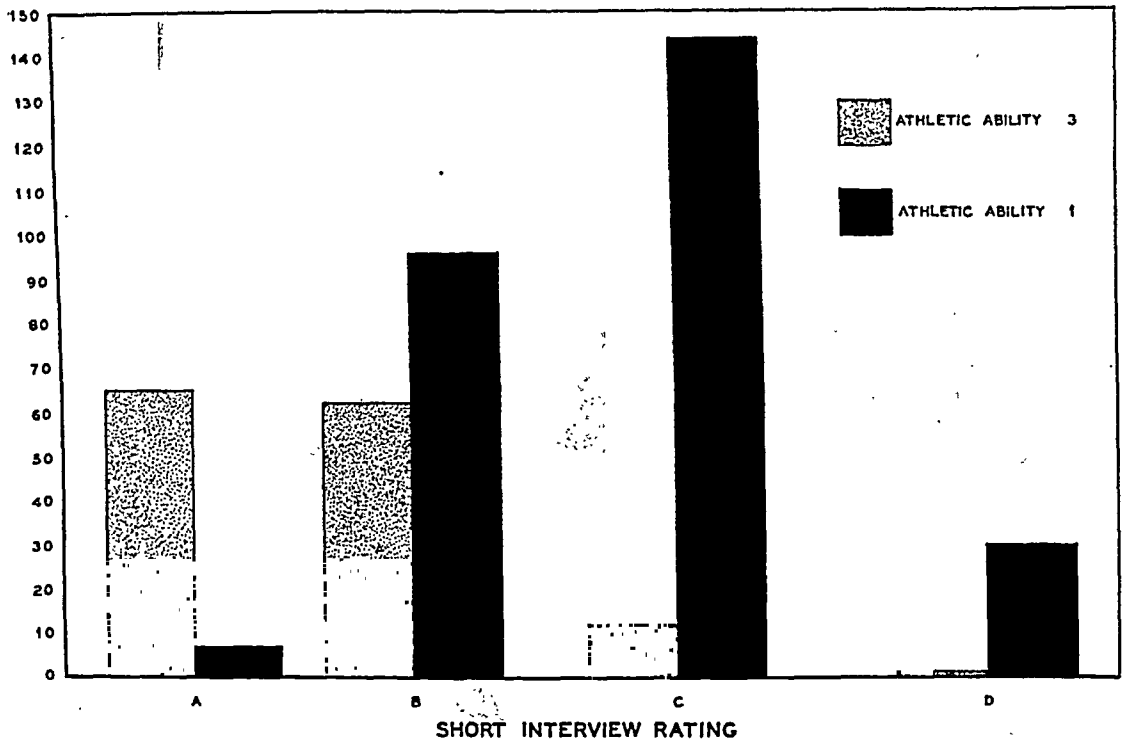
Fig. 3. Comparison of athletic ability and short interview rating for combat officership (420 candidates). In the short interview, athletic ability is rated 3 if the candidate engaged successfully in major sports, particularly contact sports like football, hockey and boxing, and if sport was a major interest. It was rated 2 if the candidate's interest was less than this and 1 if he lacked competitive spirit and avoided contact sports. The high rating for athletic ability, shown here by the dotted columns, was particularly prominent in those rated A or B for combat officership in the short interview. Those rated low for combat officership (C and D) as a rule had low ratings also for athletic ability. A similar correlation could be shown also between combat officer ratings and such traits as "strong," "alert," "dependable," etc.

instabilities of character if present are apt to appear because of the very nature of the interview.

The interview is conducted in privacy, upon a spontaneous, informal plane, and although a uniform field of facts is covered, it is kept flexible. A summary sheet is provided for checking of traits, but little writing is done during the interview.

Throughout the interview, the appearance and expression of the candidate

are under observation. It is unnecessary here to go into detail about the qualities or traits which are looked for in an officer candidate. The first impression is usually a very valid one. One is asked to judge whether the appearance of the candidate is strong or weak, inspiring or unimpressive, alert or dreamy, etc. Under this heading comes the speech which is an important
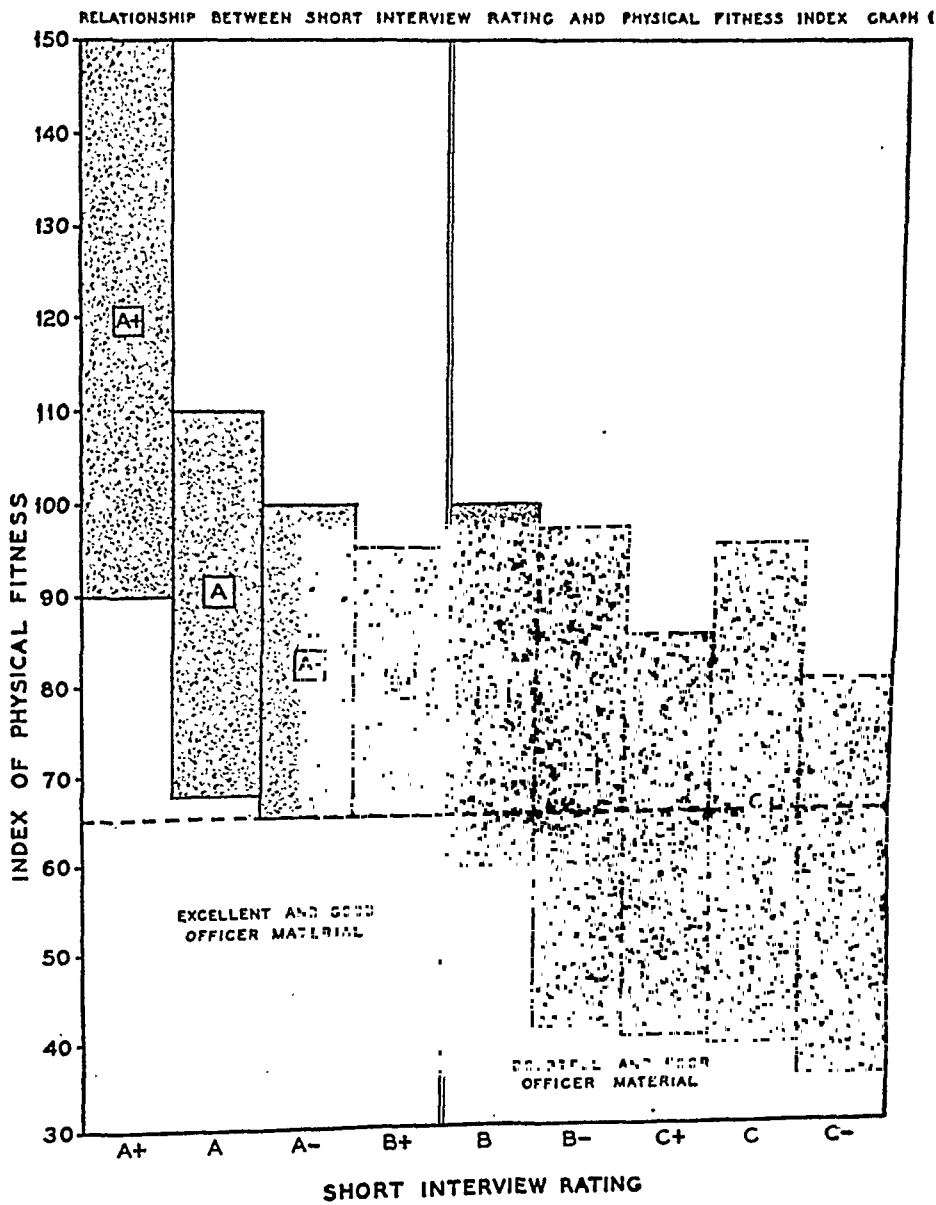
FIG. 4. Relationship between short interview rating and physical fitness index. This chart shows the range of physical fitness scores of candidates variously rated by short interview for combat officership. No individual considered excellent or good officer material scores less than 65. There is a strong tendency for those rated high for combat officership to score high in physical fitness, and for those rated low in combat officership to score lower in physical fitness. However, one does find a number of men who may score well in physical fitness who rated low in combat officership. This is because these men may have lacked other qualities of personality which would permit them to be considered first-rate officers.

consideration for an officer: is it clear or indistinct, fluent or halting, full or thin?

The manner of questioning the candidate during the interview deserves special comment. It should be borne in mind that the candidate, not the interviewer, should do most of the talking. Therefore, all questions should be brief, rather general and should give the candidate an opportunity to expand. Examples of questions are as follows:

In the case of a college student:
    "What field do you major in?"
    "How did you happen to choose that field?"
In the case of the non-college man:
    "What was your work?"
    "How did you get into it?"
And for all men:
    "What would you like to do for career, or life work?"
    "Do you like athletics?"
    "What is your favorite sport?"
    "Do you like out-door life?"
    "Are you handy with tools?"
    "What do you do in your spare time?"

It is evident that the manner in which an answer is given rather than the actual content of the answer contains the important clues to the character of the candidate. The actual occupation of the candidate affords a natural opening and this leads to choices of career and attitudes to military service. Then various activities, special skills, hobbies and accomplishments can be discussed. Lastly, social traits, health, emotional traits can then be brought out in an orderly way.

At the end of the interview, an over-all rating is given, as to whether the candidate in respect to combat officer fitness is excellent or good (A), acceptable (B), questionable or doubtful (C), or poor (D). This rating scheme can profitably be further divided. A summary sheet may then be filled out which requires checking various traits. This serves as a record, a check on the interviewer and as a basis for research.

The short interview is best given by men, preferably physicians, who have had experience in dealing with people and have some native ability for "sizing up" people. A short period of practical instruction is desirable, where actual interviews are conducted in the presence of an experienced interviewer. It is remarkable how soon and how well two people can come to identical agreement about the majority of candidates.

Figures 3 and 4 illustrate important relationships between interview findings and athletic ability and physical fitness.

III. The "Masculine Component" in the Selection of Combat Officers. The determination of masculine component and its relationship to combat officership has been the result of work by Dr. Carl Seltzer.[6] It has been

selected from many other anthropological characteristics of body build which are related to combat leadership, but it is the simplest and quickest to determine.

It is a common observation that the male body build varies from the strong, rugged, well-muscled, angular, masculine type toward the softer, rounder, less muscled, feminine type. This is true even within the normal range of men in which one does not suspect actual endocrine abnormalities. Figures 5 and 6 illustrate the anatomical characteristics which are observed in making a judgment of strong, as opposed to weak masculine components. It will be seen how intermediate degrees (medium or very weak) of masculine component can also be distinguished profitably. A four-fold scale comprising strong, medium, weak and very weak masculine component is useful.

Figures 7 and 8 illustrate the relation which exists between the masculine component of body build and (1) the physical fitness of individuals as determined by the Step Test; (2) the combat officer qualities of candidates for officer training. The estimate of masculinity can thus be a useful adjunct in the selection of combat officers.[6] Individuals who are weak in masculine component are on the whole deficient in combat officership qualities and inferior in physical fitness even after training.

DISCUSSION

From the particular example, selection of combat officers, it may be seen how different tests may be employed and the interview altered when the task is to select personnel for other occupations. A few simple basic principles for successful selection of personnel may be stated. First, there must be knowledge of ranges of traits and characteristics of people from whom the selection is to be made. Second, there must be knowledge of the particular kinds of traits and characteristics requisite to the particular task. What are the men like who have been successful in it? What are the men like who have been unsuccessful? Knowing what to look for and how to look for it is the essence of the problem. There should be recognition of the fact that "normal" people vary greatly one from another and yet remain within the range of "normal." It is appropriate, of course, to eliminate the medically

---

FIG. 5. (*Above*) Young man judged to have strong masculine component in body build. Note: (1) general angularity and ruggedness of body outline and good muscularity; (2) relatively narrow hips to shoulder breadth; (3) flatness of mammary area; (4) flatness of abdominal area; (5) interspace between thighs; (6) prominence of inner curvature of calves; (7) pubic hair running towards navel. In making actual judgments these are also observed: lack of hyperextensibility of elbows and good muscle tonus.

FIG. 6. (*Below*) Young man judged to have weak masculine component, but well within "normal" range. Note: (1) roundness and softness of body outline, without prominent musculature; (2) relatively greater hip breadth to shoulder breadth; (3) fullness in mammary area; (4) feminine abdominal protuberance; (5) approximation of thighs; (6) greater outer curvature of calves; (7) lateral distribution of pubic hair. In making actual judgments there are to be observed also the arms carried with an angle at the elbow (hyperextensibility), and poor muscle tonus.
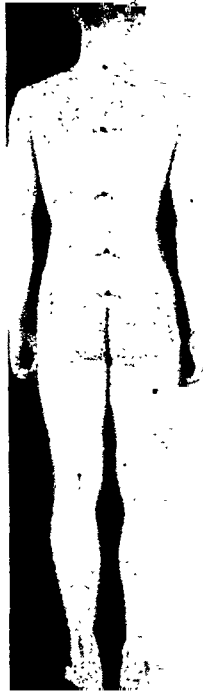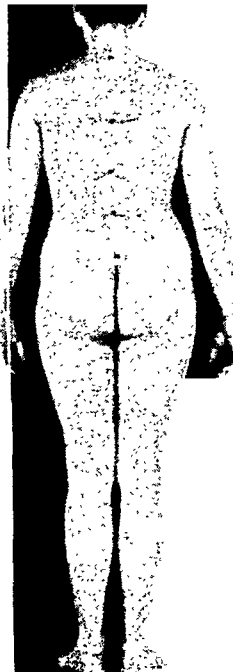
unfit, but the work of selection has not been completed until there have been distinguished among the medically fit those whose traits are adapted to the task at hand.

There is a great need for better diagnosis of people.   Tests of many
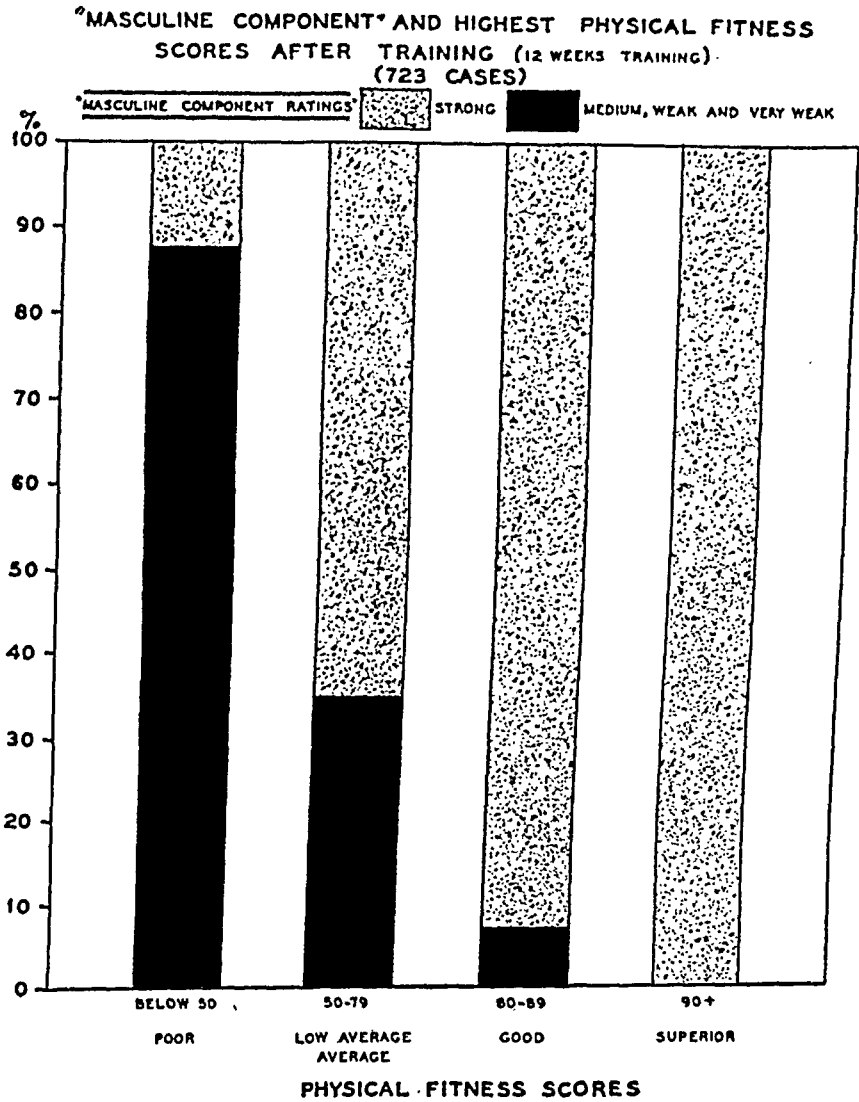
FIG. 7. "Masculine component" and highest physical fitness scores (723 cases). The light part of the columns represents the per cent of candidates having strong masculine component; the black parts of the column those having medium, weak or very weak masculine component. All of those scoring over 90 for physical fitness had "strong masculine component" and 93% of those scoring 80-89. Weaker masculine component was prominent in those scoring less in physical fitness.

kinds have been developed, but no test as yet can take the place of seeing and talking to the individual. Subjective feeling about an individual, allied to that of the physician when he makes a medical diagnosis is still necessary. But the physician's diagnosis, subjective or intuitive though it may be, is based on years of experience with patients and is ultimately factual,

although the facts and factors are too complex to yield to mathematical analysis.   As progress is made, however, and tests develop, there is less necessity for subjective diagnosis.   The procedure in the "diagnosis" of normal personalities seems to be the same, and as knowledge advances, it may become

"MASCULINE COMPONENT" AND COMBAT OFFICER RATINGS
(632 CASES)
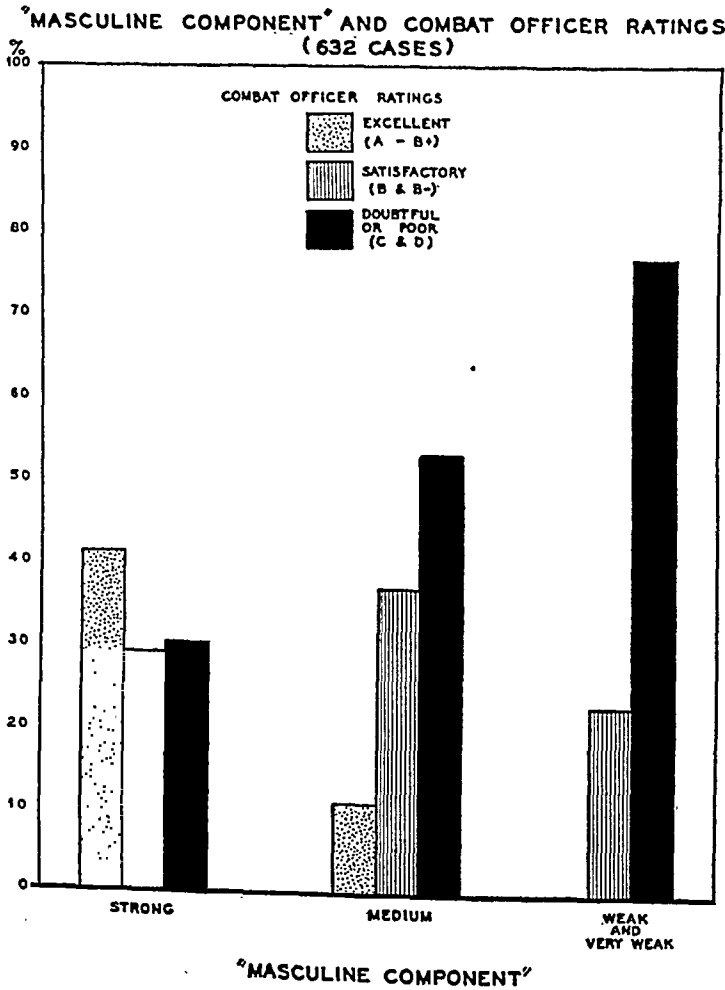
FIG. 8.   "Masculine component" and combat officer ratings (632 cases). This chart shows the relationship between masculine component and combat officer ratings. The combat officer ratings were made by army or navy officers in charge of the R.O.T.C.   In the first group with "strong masculine component" 41 per cent were rated as excellent officer candidates.   In the group with "medium masculine component" only 11 per cent were rated as excellent officer candidates, 54 per cent as doubtful or poor.   Of the group with "weak or very weak masculine component" no men were rated excellent for combat officership, 77 per cent were rated doubtful or poor.

not too difficult to assign people accurately to appropriate training for particular tasks, careers and occupations.

BIBLIOGRAPHY

1. Studies in the Relationship of Personality and Field of Work: Selection of Combat Officers, 1943, Harvard University Press, Cambridge, Mass.

2. JOHNSON, R. E., and BROUHA, L.: Pulse rate, blood lactate and duration of effort in relation to ability to perform strenuous exercise, Rev. canadienne de Biol., 1942, i, 171–177.
3. JOHNSON, R. E., BROUHA, L., and DARLING, R. C.: A test of physical fitness for strenuous exertion, Rev. canadienne de Biol., 1942, i, 491–503.
4. BROUHA, L., GRAYBIEL, A., and HEATH, C. W.: The step test. A simple method of measuring fitness for hard muscular work in adult man, Rev. canadienne de Biol., 1943, ii, 86–92.
5. BROUHA, L., and HEATH, C. W.: Resting pulse and blood pressure values in relation to physical fitness, New England Jr. Med., 1943, ccxxviii, 473–477.
6. SELTZER, C. C., and BROUHA, L.: The "masculine" component and physical fitness, Am. Jr. Phys. Anthrop., 1943, i, 95–108.

POST–CONCUSSION SYNDROME—A CRITIQUE *

By D. Denny-Brown, M.B., F.R.C.P., *Boston, Massachusetts*

Though head injuries are usually considered to be the province of the surgeon, the physician, as Richard Bright [1] remarked over a century ago, is so commonly called upon to alleviate their after-effects and has so often to take them into account in relation to general disease, that it behooves him to interest himself in their mechanism.

Traumatic disorder of the nervous system is in general of a kind that is at its worst immediately following the injury, and thenceforth lessens in severity as reparation is made. This is true of the paralysis due to damage to the cerebral cortex, to injuries of the cranial nerves, and to such hemorrhage as may be directly provoked. There are, it is true, some immediate complications in the first few days, such as epidural hemorrhage, acute subdural hematoma, and meningitis, which appear as separate entities after the event. These, however, are the true surgical anxieties and are little the physicians' concern.

By the time the patient is referred to the physician he is usually beyond the stage of these immediate surgical hazards, and the first questions that arise in the mind of the physician are somewhat as follows. Is the patient's present trouble the residue of some greater disorder precipitated by the head injury? Or is it something developing afresh, and if so, is it due to the trauma or to some unrelated disease? Let us list the chief general cerebral disorders which occur in the convalescent period after head injury.

Group I

Disorders which are maximal in degree immediately after head injury and tend to progressive improvement

Paralysis
Intellectual impairment (stupor, confusion)
Headache (local, usually occipital, worse on movement)
Vertigo

Group II

Disorders which appear at an interval of weeks and tend to increase in severity

Epilepsy
Stupor, hemiplegia (chronic subdural hematoma)
Bouts of headache, dizziness, loss of concentration ("post-concussion syndrome")
Psychoneurosis

One of the commonest after effects of head injury is the "post-concussion syndrome," and I have put it unhesitatingly in the second group. Its place here is little recognized; in fact, much of the confusion surrounding the sub-

ject is derived from lack of appreciation of the delay in onset. It does not appear until the patient is fit to attempt mental and physical exertion, and its periodic nature is then related to attempted exertion. The syndrome has acquired a large literature since attention was first drawn to it in surgical writings (Hutchinson, 1877).[3] It has been reviewed by Symonds,[4, 5] Strauss and Savitsky,[8] Schilder,[9] Russell,[10] and Schaller [11] in recent years.

The bouts of throbbing, sometimes piercing ache are usually of brief duration, and are localized diffusely to alternate sides of the head. They are precipitated by effort, both physical and mental, and when present the headache is markedly influenced by posture. It is associated with dizziness of a non-specific, vague, rocking kind, and with difficulty in mental concentration. There is often insomnia and depression with emotional lability. When these latter emotional symptoms are associated with a constant dull pressing sensation in the head instead of the bouts described above the condition is more clearly a psychoneurotic depression and not the true post-concussion syndrome. All investigators have remarked on the relative constancy of the more characteristic symptoms in patients who have had no opportunity for collaboration, a constancy which tends to indicate some identity of mechanism of symptom production. All authors are agreed on the psychoneurotic aspect of the reaction, yet almost all have seen it follow severe head injury in a stable personality sufficiently often to feel that some organic basis is possible. A large number of clinical tests have at various times been advocated as objective criteria of the condition. None, however, has stood the test of time (see Strauss and Savitsky [8]).

It has been noted by many that patients who suffer severe lacerations of the brain often fail to develop the characteristic syndrome. I have indicated elsewhere,[15] however, that it tends to develop late in these patients, a fact more obvious to the neurologist and physician than to the surgeon.

A number of contradictory statements in the literature arise from confusion of types of headache and circumstances of origin of the syndrome. It is necessary to point to some obvious discrepancies. A recent paper by Malone [2] claims relief for the post-concussion syndrome by treatment with prostigmine. This investigator summarizes the effect of this drug in a table of 10 cases. Two cases are singled out for mention in greater detail. The first is that of a 40 year old male who had suffered a head injury two years previously and had since had attacks of "dizzy spells," each of which necessitated bed rest for two or three days. He did not suffer from headache. Such prolonged attacks are not a usual post-concussional symptom and more closely resemble Ménière's syndrome. The second case reported in detail was a housewife, aged 59, who sustained a head injury in January 31, 1940, since which time she had suffered from "frontal and occipital headaches, photophobia, almost constant dizziness, and occasional diplopia." The condition persisted until February 22, though she had remained in bed. Institution of prostigmine treatment was then accompanied by subsidence of the symptoms, so that by March 3 the patient was able to be about. In Sep-

tember she had had further symptoms. This type of headache and dizziness is that present in almost all cases of moderate head injury (see Group I) and particularly in patients who have had traumatic subarachnoid hemorrhage. Its natural course is a gradual subsidence in some two to six weeks depending upon its severity. The subsidence in just over four weeks in Malone's case is, therefore, not particularly surprising. But to advance such a condition as the post-concussion syndrome is wholly confusing. That point of view is not at all an uncommon one.

There are two views which have wide support at the present time. One is derived from the investigations of Penfield,[16] who claimed that he had demonstrated subdural adhesions in patients with post-traumatic headache; the other is exemplified by the view of Russel who is quoted [13] as saying: "Whereas in the last war the soldier who cannot 'stand the gaff' considered himself a victim of 'shell shock' and might well show hysterical phenomena, paralyses or anesthesias; in this war he has learned that the complaint of headache following a blow on the head is apt to serve as entitlement to invalidism and discharge." The first explanation, Penfield's, throws all the emphasis on the scar. The second implies that all is self-motivated.

In my own experience with a large number of military cases as well as the usual neurologist's experience with civilian cases, neither of these views meets the facts. Patients with subdural scars seldom have headache and this headache is then localized to the region concerned. The Penfield and Norcross [12] test of the presence of subdural air following lumbar insufflation is positive in many patients without head injury, as demonstrated conclusively by Lemere and Barnacle.[14] On the other hand a post-concussion syndrome following very severe head injury can often be related to impaired intellectual capacity.[15] The syndrome is then a reaction which occurs whenever the patient attempts something beyond the limit of his powers of cerebration. The difficulty here is that such impairment can be conclusively demonstrated only by well conducted intelligence tests, though any simple appraisal of memory and judgment should suffice for clinical purposes.

The post-concussion syndrome can also occur as a pure psychoneurosis following trivial head injury, but the mechanism is seldom one of malingering. Careful history taking reveals most commonly that the patient has had previous liability to neurosis, and that some stress or exhaustion preceding the head injury had primed the occurrence of another psychoneurotic manifestation (Denny-Brown [15]). Next in order of frequency as underlying cause of a psychoneurotic type of post-concussion syndrome following head injury is the addition of undue physical or mental stress in the weeks following head injury. The man who breaks down on too early return to work or duty comes under this category, and the reaction may be in no way attributable to failure on his part. The basic defect is then "organic." Thus, whatever the mechanism of production of these symptoms which make up the syndrome, the underlying failure may be psychoneurotic or an organic remainder from the injury or a combination of the two.

It is, therefore, concluded that the post-concussion syndrome is a reaction to circumstance and, as such, appears as a separate event at an interval after injury. Thus, it has to be distinguished chiefly from epilepsy and from chronic subdural hematoma. The stupor and increasing paralysis due to the latter should be sufficiently distinct to avoid confusion. In rare cases a subdural hematoma is the cause of the mental inadequacy which leads to the syndrome. Secondly, it is emphasized that the underlying cause may be any or all of three factors—severe general damage to the brain leaving intellectual impairment, constitutional liability to psychoneurotic reactions, and undue physical or mental stress in the post-traumatic period.

Careful history taking will resolve the importance of these factors in the individual case. It is found that physicians are chiefly troubled by the definition of intellectual impairment. However, if it is remembered that this is one of the features that belong to the Group I mentioned earlier, and that, therefore, it is derived from some greater disorder immediately following the injury, the indications should be clear. It is the patient who has been unconscious for a long period, confused and disoriented for many days or weeks, who is found later to suffer intellectual impairment, never the man who was unconscious for only minutes or hours. A reliable history of the injury will, therefore, either rule out or indicate this possibility.

Special procedures such as electroencephalography and air encephalography are of great value in demonstrating localized atrophy and the focus of epilepsy. They have been of little value in the differential diagnosis of the post-concussion syndrome because the changes, if any, are slight in such cases, are not greater than is present in many normal people who have never had a head injury, and even when known to follow head injury are not consistently associated with symptoms. The milder changes demonstrated by these methods do not form a disability unless supported by other evidence (Denny-Brown [15]).

It may be of topical interest to record here that all the cases of post-concussion syndrome following close exposure to the blast of bomb or shell seen by me followed an initial psychoneurotic disturbance, without brain damage. Conversely, two patients within 12 feet of the burst of large bombs were not concussed, though receiving other brain injury from splinters for which they came under our care. They did not suffer from the syndrome.

The effectiveness of treatment of the post-concussion syndrome depends on accurate assessment of its underlying cause or causes. The success achieved in a British hospital for military and R. A. F. head injuries, with which the author was associated for its first 18 months, may be judged from figures published by Symonds [6] from a follow-up of the first 1,000 cases. These patients on admission to the hospital were suffering from disability lasting six weeks or more after a head injury. There were 871 men on whom a long period follow-up was possible. Sixty-seven per cent were returned to active service duty successfully (i.e., maintained satisfactory duty for a period of months). A severe psychoneurotic type of disorder was

found to be as refractory to treatment as a severe organic disorder, but psychoneurotic factors in men of stable personality responded well to treatment.[15, 7] A test of heavy exercise, for example digging or sawing wood, is an absolute necessity before final discharge from hospital to duty if relapse is to be avoided.

The type of disorder most difficult to treat is lowering of intellectual capacity, though much can be accomplished by adjusting such patients' occupation so as to bring it within their cerebral limitation. Within the armed forces such adjustment can be accomplished only if the ultimate defect is small. It is, therefore, of the greatest importance to make early and reliable estimation of prognosis in this respect. A valuable criterion is the duration of post-traumatic amnesia, i.e., the duration of time from the injury to the patient's first current memory of later events. Though the time interval is based on subjective evidence, it can be checked against records of his state in the relevant period which should have shown coma progressing to confusion and disorientation with lack of insight. The correlation of duration of post-traumatic amnesia (P. T. A.) is well brought out in Symonds' analysis [6] of follow-up cases. When the P. T. A. was less than one hour the percentage of successful return to duty was 77. For P. T. A. of between one and seven days 62 per cent returned. Following a P. T. A. of more than one week only 52 per cent returned. The chief disabilities due to laceration, namely epilepsy or paralysis (including cranial nerve palsies) have little or no correlation with duration of amnesia, for in penetrating war wounds loss of consciousness is usually brief or does not occur. Such disabilities, however, are less difficult to assess, and the above figures serve to show the close relationship between the severity of general cerebral injury indicated by P. T. A. and residual damage in intellectual capacity.

Finally, the close similarity between the post-concussion syndrome in all its aspects and the so-called "effort syndrome" may be emphasized. Both might be defined as special forms of nervous reaction following at an interval either the possibility or the actuality of damage to the organ concerned.

BIBLIOGRAPHY

1. BRIGHT, R.: Reports of medical cases, 1831, Longman, London, vol. ii, part 1.
2. MALONE, J. Y.: Head injuries: a new treatment for post-concussional headaches and dizziness: preliminary report, Jr. Am. Med. Assoc., 1942, cxix, 861–863.
3. HUTCHINSON, J.: Illustrations of clinical surgery, 1877, J. A. Churchill, London, vol. 1.
4. SYMONDS, C. P.: The effects of injury upon the brain, Lancet, 1932, i, 820.
5. SYMONDS, C. P.: Concussion and contusion of the brain and their sequelae. Chapter 4 in BROCK's Injuries of the skull, brain and spinal cord: neuro-psychiatric, surgical and medico-legal aspects, 1940, William Wood and Company, Baltimore.
6. SYMONDS, C. P.: Differential diagnosis and treatment of post-contusional states, Proc. Roy. Soc. Med., 1942, xxxv, 601–607 (Section of Neurology pp. 25–31).
7. SYMONDS, C. P., and RUSSELL, W. R.: Accidental head injuries: prognosis in service patients, Lancet, 1943, i, 7–10.
8. STRAUSS, I., and SAVITSKY, N.: Head injury: neurologic and psychiatric aspects, Arch. Neurol. and Psychiat., 1934, xxxi, 893–955.

9. SCHILDER, P.: Neuroses following head and brain injuries. Chapter 12 in BROCK's Injuries of the skull, brain and spinal cord: neuro-psychiatric, surgical and medico-legal aspects, 1940, William Wood and Company, Baltimore.

10. RUSSELL, W. R.: Cerebral involvement in head injury: study based on examination of 200 cases, Brain, 1932, lv, 549–603.

11. SCHALLER, W. F.: After effects of head injury: Post-traumatic concussion state (concussion, traumatic encephalography) and post-traumatic psychoneurotic state (psychoneurosis, hysteria): Study in differential diagnosis, Jr. Am. Med. Assoc., 1939, cxiii, 1779–1785.

12. PENFIELD, W., and NORCROSS, N. C.: Subdural traction and post-traumatic headache: study of pathology and therapeusis, Arch. Neurol. and Psychiat., 1936, xxxvi, 75–94.

13. RUSSEL, C., quoted by PENFIELD, W.: Clinical notes from a trip to Great Britain, Arch. Neurol. and Psychiat., 1942, xlvii, 1030–1036.

14. LEMERE, F., and BARNACLE, C. H.: Encephalography: a review of eight hundred encephalograms, with special reference to subdural air, Arch. Neurol. and Psychiat., 1936, xxxv, 990–1001.

15. DENNY-BROWN, D.: The sequelae of war head injuries, New England Jr. Med., 1942, ccxxvii, 771–780 and 813–821.

16. PENFIELD, W.: Chronic meningeal (post-traumatic) headache and its specific treatment by lumbar air insufflation, Surg., Gynec., and Obst., 1927, xlv, 747.

DISABLING CHANGES IN THE HANDS RESEM-
BLING SCLERODACTYLIA FOLLOWING
MYOCARDIAL INFARCTION *

By Alf C. Johnson, M.D., F.A.C.P.,
Great Falls, Montana

Disabling trophic changes and deformities of the hands and fingers resulting from local ischemia are well recognized sequelae of "external" vasoconstriction from the splinting of injured hands and of "intrinsic" vasoconstriction from overactivity of the sympathetic nervous system. Scleroderma and sclerodactylia develop in Raynaud's disease and are regarded as among its most troublesome complications.[1] Similar trophic changes in the hands occurring as a sequel of acute myocardial infarction in 39 of 178 (21.8 per cent) consecutive cases of myocardial infarction are the subject of this report.

The first case (Case 18 in table 1), was referred early in 1937 by Dr. F. R. Schemm, an associate in the Great Falls Clinic, and was regarded as a case of "rheumatoid arthritis." When three similar cases were encountered that year on the cardiology service they were referred by him with the idea that a clinical syndrome might be being overlooked.

The appearance and course of these alterations were not similar to those seen in arthritis. The changes resembled very closely, however, those described as occurring in the hands of patients suffering with scleroderma and of patients having an abortive form of Raynaud's disease. In the literature,[2, 3] under the term sclerodactylia (hard fingers), is a description of a syndrome which is the prototype of the changes observed in the fingers of the four cases seen in 1937. No reference in the literature available in 1937 is made to any association between myocardial infarction and sclerodactylia, unless this sentence of Barker's[3] is significant: "I have found in most of my cases (of scleroderma) which develop late in life, organic disease of the heart and vascular system."

THE CHANGES IN THE HANDS

The first symptoms which attracted the attention of the patient and which appeared from three to 16 weeks after the acute myocardial infarction in this series were pain and stiffness of the fingers. Uniform, firm, bilateral, symmetrical swelling of the entire hands including the fingers appeared. The swelling did not pit on pressure. The skin became smooth and tight, and the normal wrinkles in the skin were more shallow or were entirely obliterated. This was true especially of the transverse wrinkles over the dorsum of the fingers. Color changes in the hands occurred, varying from

TABLE I

Case No.	Age and Sex	Date of Infarction	EKG Findings	Anginal Syndrome	Radiation Anginal Pain	Interval Between Infarction and "Joint" Symptoms	"Joint" Affected First	Early Status						Present Status				Remarks
								Distribution of Pain					Previous Rheumatic History	Hands		Cntrtn Palmar Fascia	Stiff Shoulders	
								Shoulders		Hands		Other Joints		Atrophy	Limitn Motion			
								R	L	R	L							
1.	47 M	2-25-41	Diagnostic of infarction. Anterior	Present	L arm	6 weeks	"Hands"	0	+	+	+	0	0	++	++	++	0	Markedly limited by angina of effort and stiffness of hands. No foci.
2.	48 M	9-1-40	Diagnostic of infarction. Posterior	Present	L arm	12 weeks	R hand	0	+	+	+	R knee	0	+	+	0	0	Working as chef. Foci: Tonsils and teeth. (Has bronchial asthma.)
3.	58 F	10-31-40	Compatible with post. Infarction	Present	No radiation	6 weeks	R hand	+	+	+	+	0	0	++	++	++	0	Cardiac cripple. Cholecystostomy 1941. No other foci.
4.	63 F	4-27-39	Diagnostic of infarction. Anterior	Present	R shoulder	4 weeks	R shoulder	+	0	+	+	0	0	++++	+++	+++	0	Partially disabled by hands and heart. No foci.
5.	70 F	3-21-40	Diagnostic of infarction. Anterior and posterior	Present	No radiation	4 weeks	Hands	+	0	+	+	0	0	+++	++++	+++	+	Disabled by hands and heart. Death 10-2-40. agranulocytosis. No foci.
6.	73 F	10-2-37	Old EKG shows myocardial disease. No EKG taken since infarction	Present	No radiation	10 weeks	R shoulder	+	+	+	+	Knees and elbows	Rh. Fever as child. Hypertr. arth. for 15 yrs.	++	++	++	+	No other foci. Cholecystectomy 8-11-37. Hypertrophic arthritis present.
7.	53 M	5-21-40	Diagnostic of infarction. Anterior	Present	L arm	9 weeks	Shoulders	0	+	+	+	0	0	+++	+++	+	0	Cardiac cripple. No foci. Moderate subluxation fingers.
8.	64 M	10-13-39	Diagnostic of infarction. Anterior	Present	R arm	8 weeks	R shoulder	+	0	+	+	R knee	0	+	+	+	+	Adenoma of prostate, mild cystitis. Sudden death Sept. 1940.
9.	68 M	6-15-37	Diagnostic of infarction. Anterior	Present	Both shoulders	8 weeks	R shoulder	+	+	+	+	0	0	+++	+++	++	+	Cardiac cripple—hands badly disabled. No foci.

TABLE I—Continued

Case No.	Age and Sex	Date of Infarction	EKG Findings	Anginal Syndrome	Radiation Anginal Pain	Interval Between Infarction and "Joint" Symptoms	"Joint" Affected First	Early Status — Distribution of Pain					Previous Rheumatic History	Present Status — Hands		Cntrtn Palmar Fascia	Stiff Shoulders	Remarks
								Shoulders		Hands		Other Joints		Atrophy	Limitn Motion			
								R	L	R	L							
10.	39 M	2-12-41	Compatible with recent infarction. Qa deep. S/T1 depressed	Present	Both arms	6 weeks	Both shoulders	+	+	+	+	0	0	0	0	0	0	Activity restricted because of heart. No other disability. No foci.
11.	60 F	1-25-41	Diagnostic of infarction. Posterior	Present	Both arms	5 weeks	R shoulder	+	+	+	+	0	0	+	+	+	+	Activity markedly limited by angina of effort.
12.	55 F	1-3-38	Diagnostic of infarction. Atyp. post. Atyp. LBBB QRS .18 sec.	Present	L arm	3 weeks	R shoulder	0	+	+	+	0	0	++	+	0	++	Activity limited by angina of effort to light housework.
13.	51 M	6-26-40	Diagnostic of infarction. Posterior	Present	L arm and neck	6 weeks	L shoulder	0	+	+	+	0	0	+++	+++	+	0	Disabled by heart and hands. No foci.
14.	80 M	9-21-40 (several infarctions)	Diagnostic of infarction. Anterior LBBB QRS .18 sec.	Present	No radiation	Indefinite	Indefinite	0	0	+	+	Vague	0	+	++	0	+	Died 10-2-41—pulmonary embolism. No foci.
15.	54 F	Fall 1937	No definite abnormalities. LVP. QRS .10 sec.	Present	L arm and shoulder	12 weeks	L shoulder	0	+	+	+	0	0	+	+	+	+	Limited to light housework by heart and hands. No foci
16.	51 F	5-11-39	Diagnostic of infarction. Posterior	Present	Both shoulders	8 weeks	R shoulder	+	0	+	+	0	Rh. fever age 6	++	++	++	0	Limited by angina of effort—stiffness right hand. No foci.
17.	56 M	4-2-41	Not taken	Present	L arm	12 weeks	L shoulder	0	+	+	+	0	0	++	++	0	0	Activity markedly restricted by angina of effort.
18.	60 M	12-4-36	Diagnostic of infarction. Anterior	Present	L arm	12 weeks	L shoulder	0	+	+	+	0	0	+++	+++	++	+	Completely disabled by angina of effort. Marked contraction deformity. No focus.

TABLE I—*Continued*

Case No.	Age and Sex	Date of Infarction	EKG Findings	Anginal Syndrome	Radiation Anginal Pain	Interval Between Infarction and "Joint" Symptoms	"Joint" Affected First	Early Status — Distribution of Pain — Shoulders R	L	Hands R	L	Other Joints	Previous Rheumatic History	Present Status — Hands — Atrophy	Limitn Motion	Cntrtn Palmar Fascia	Stiff Shoulders	Remarks
19.	61 M	1-9-41	Not diagnostic of; compatible with infarction. Low T1; inverted T4; notched T4	Present	L shoulder	6 weeks	"Hands"	0	+	+	+	0	0	++	++	+	+	No foci. Activities much restricted by hands and anginal syndrome.
20.	60 M	3-16-38	Compatible with infarction, posterior. (Taken 6-3-38)	Present	Both arms	16 weeks	Both shoulders	+	+	+	+	0	0	+	+	0	0	Moderate restriction of activities because of angina of effort.
21.	66 M	(6-15-39) and *3-12-41*	Diagnostic of infarction. Anterior	Present	Both arms	4 weeks (after 3-12-41)	R shoulder	+	+	?	?	0	St. Vitus Dance age 12	?	?	?	+	No foci. Last seen 4-7-41. Died suddenly 5-29-41. See autopsy report.*
22.	68 F	Dec. 1938 Silent infarction	Diagnostic of infarction. Posterior. A-V dissociation. Aur. 70, ventr. 45	Present	Both shoulders	Approx. 5 weeks	L shoulder	+	+	+	+	0	0	++	+++	++	+	Activities limited because of angina of effort and stiffness of hands. No foci.
23.	57 M	1-2-38	Diagnostic of infarction. Ant. and post. QRS .16 sec. LBBB	Present	L arm	12 weeks	L shoulder	0	+	+	+	0	Rh. fever age 16	+	+	+	+	Activities limited because of angina of effort and stiff shoulders.
24.	62 M	4-10-41	Diagnostic of infarction. Location indeterminate	Present	Both arms	10 weeks	Both shoulders	+	+	+	+	0	0	+	+	0	0	Activity limited because of angina of effort.
25.	71 F	9-18-39	Compatible with infarction. (T1 inverted)	Present	shoulders	12 weeks	Both shoulders	+	+	+	+	R knee	Hypertr. arthr. for 19 yrs.	+	++	++	+	Markedly limited because of angina of effort and stiffness of hands. No foci.

* Died in California; autopsy report through courtesy of Drs. J. E. Kohler and J. M. Askey: Rheumatic valvular disease with 20 per cent stenosis mitral valve and deformed aortic valve. Right coronary artery site of partially recanalized occlusion 1 cm. in length. Fresh red thrombus middle third of left descending branch of very sclerotic left coronary artery. Left shoulder joint removed in toto; no gross or microscopic pathological changes.

TABLE I—*Continued*

Case No.	Age and Sex	Date of Infarction	EKG Findings	Anginal Syndrome	Radiation Anginal Pain	Interval Between Infarction and "Joint" Symptoms	"Joint" Affected First	Early Status — Distribution of Pain — Shoulders R	Shoulders L	Hands R	Hands L	Other Joints	Previous Rheumatic History	Present Status — Hands — Atrophy	Limitn Motion	Cntrtn Palmar Fascia	Stiff Shoulders	Remarks
26.	73 F	6-9-41	EKG not taken	Present	L shoulder	8 weeks	Both shoulders	+	+	+	+	R knee	"Rheumatism" 1929 (Pain R knee)	0	+	+	+	Does own housework. Has mild hypertrophic arthritis. No foci.
27.	55 F	Fall 1939 (Multiple infarctions)	Compatible with infarction. QRS .16 sec. Auric. Fibr. T₁, T₂ low	Present	No radiation	Indefinite, established by Spring of 1940	L shoulder	0	+	+	+	0	0	+	+	0	+	Markedly limited by cardiac insufficiency. Angina mild. No foci.
28.	79 F	10-1-38	Diagnostic of infarction. Prob. ant. (3 leads only)	Present	Arms and shoulders	4 months	Shoulders	+	+	+	+	0	"Rheumatism" R foot age 60	+	+	0	+	Limited activity. No foci.
29.	46 M	10-5-40	Diagnostic of infarction. Anterior	Present	Arms and elbows	4 months	Shoulders	0	+	+	+	0	0	0	+	0	0	Moderate limitation of activities because of angina of effort.
30.	46 M	5-1-40	Not diagnostic of infarction. Compatible with myocardial disease	Present	Arms	3 months	Shoulders	+	+	+	+	0	0	+	.	0	+	No foci; no particular limitation of clerical activities.
31.	56 M	8-19-41	Diagnostic of infarction. Anterior. Atyp. LBBB QRS .16 sec. (Auric. Fib.)	Present	No radiation	8 weeks	Hands	0	0	+	+	0	0	0	+	0	0	No foci; activities restricted because of recent infarction.
32.	59 F	(Earliest) 6-6-34, 9-16-39, 6-30-39	Diagnostic of infarction. Posterior Anterior	Present	Both arms	16 weeks	L shoulder	0	+	+	+	0	R knee	++	++	0	0	Intermittent claudication right calf 4-5-37; diabetes mellitus. Death 5-31-40.
33.	45 F	3-6-41	Diagnostic of infarction. Ant. and post.	Present	Both arms	16 weeks	Hands	0	0	+	+	0	Rh. fever age 6	+	++	0	0	Completely disabled by heart—increasing stiffness of hands. No foci.

TABLE I—Continued

Case No.	Age and Sex	Date of Infarction	EKG Findings	Anginal Syndrome	Radiation Anginal Pain	Interval Between Infarction and "Joint" Symptoms	"Joint" Affected First	Early Status Distribution of Pain					Previous Rheumatic History	Present Status				Remarks
								Shoulders		Hands		Other Joints		Hands		Cntrtn Palmar Fascia	Stiff Shoulders	
								R	L	R	L			Atrophy	Limitn Motion			
34.	64 M	6-26-41	Diagnostic of infarction. Anterior	Present	Right arm	12 weeks	R shoulder	+	+	+	+	0	0	+	+	0	+	Limited by cardiac insufficiency.
35.	47 M	7-16-41	Diagnostic of infarction, location indeterminate	Present	None	3 weeks	Hands	+	+	+	+	0	0	+	++	0	0.	Limited by cardiac insufficiency. Has cardiovascular syphilis.
36.	70 F	9-21-41	Diagnostic of infarction. Posterior	Present	Both arms	6 weeks	Hands	+	+	+	+	0	Hypertrophic arthritis of R hand	++	+++	+	+	Limited activity.
37.	72 F	8-6-41	Diagnostic of infarction. Posterior. Auricular fibrillation	Present	None	5 weeks	Hands	0	0	+	+	0	0	+	+	+	0	Died suddenly 6-2-42.
38.	74 M	12-30-41	Diagnostic of infarction. Anterior	Present	R arm	8 weeks	R shoulder	+	+	+	+	0	0	+	+	+	+	Moderate limitation of physical activities.
39.	46 M	3-1-42	Diagnostic of infarction. Anterior. Right ventricular preponderance	Present	None	8 weeks	Hands	0	0	+	+	0	0	+	++	0	0	Marked limitation of physical activities because of status asthmaticus and cor pulmonale.

an erythema to different grades of cyanosis. The hands and fingers were cold to the touch, and no consistent moistness, dryness, or sensory changes were noted. No striking changes were present in the volume of the pulse in the radial or brachial arteries, although, for the most part, these vessels showed varying degrees of thickening and sclerosis. The fingers could never be fully extended or flexed, and when they were manipulated pain accompanied the increased motion. Effusion in the joints and crepitation never developed. No nodules or nodes were observed except in those patients who had a preëxisting hypertrophic arthritis. These characteristics were noted in the early stages of all the cases and varied only in degree.

With the passage of time and regardless of therapy, the swelling of the fingers and hands subsided, but no particular changes occurred in the pain or stiffness of the fingers. The skin which first appeared thin and glossy now became thickened and dull in color, sometimes bronzed. The joints and bony prominences of the hands and fingers were more apparent because of shrinkage of the soft tissues over the phalangeal shafts. Movements of the fingers were limited and painful, and neither complete flexion nor extension could be accomplished. The soft tissues overlying the phalanges on the dorsal surfaces appeared to become more tightly attached to the underlying structures. Soft tissue atrophy made the metacarpals stand out and the tendons become more prominent. The contracture of the palmar fascia was not as apparent at this stage as later in the course of the disease. In some longstanding cases the roentgenograms showed disuse atrophy of the bone. These characteristics of the hands and fingers were constant in the later stages in all cases although variable in degree in individual patients.

The functional capacity of the fingers was quite variable. Some patients developed severe contractures of the fingers, whereas others had few residual deformities and little impairment of motion, though function earlier may have been greatly impaired. In the more severe cases the hands of these patients felt stiff, withered and wooden, and when grasped one felt that all softness, pliability and flexibility had been lost, justifying the descriptive term sclerodactylia or "hard fingers." The changes never progressed further and in many the function, appearance, and texture of the hand approached the normal. Areas of gangrene and the formation of ulcers were never observed. No pain or impaired function of the elbows or wrists ever occurred. No other joints of the body, except the shoulders, changed in function or gross appearance. No change occurred in any preëxisting arthritis or disability in other joints.

The syndrome described above most closely resembled descriptions of the changes recorded as occurring in the hands and fingers found in the sclerodactylia of scleroderma and Raynaud's disease.[1, 2, 3]

CLINICAL MATERIAL AND OBSERVATIONS

The 39 patients in this series seen in the past five years were encountered in the cardiology service and were referred to the arthritis service where they

were followed and treated because of the painful disability of the hands following their myocardial infarctions. They came from a group of approximately 178 cases of myocardial infarction in a series of approximately 375 consecutive cases of grossly evident heart disease. In this series of 375 cases *of all forms* of severe heart disease no painful disability of the hands of this nature developed unless a myocardial infarction had occurred.

Diagnosis of myocardial infarction was made on the basis of a typical clinical syndrome in all patients and electrocardiographic studies which were compatible with, or diagnostic of, myocardial infarction in all but five patients. Electrocardiographic studies did not support the clinical diagnosis in two patients, and no electrocardiograms were made in three patients. In these five patients the clinical diagnosis of myocardial infarction was supported by the presence of leukocytosis and fever and the development of such phenomena as a severe anginal syndrome, a pericardial friction rub, myocardial failure, emboli, etc.

Table 1 summarizes the clinical observations on the 39 cases. Four of these cases are presented in greater detail, with pertinent photographs, roentgenograms and electrocardiograms.

SUMMARY OF DATA FROM TABLE 1

1. *Age and Sex:* The average age in years of the 39 patients in this series was 58.3. Twenty-three patients were male and 16 were female.

2. *Electrocardiographic Findings:* Electrocardiographic studies were compatible with, or "diagnostic" of, myocardial infarction in all but five patients. Three of these patients had no electrocardiograms and the electrocardiographic study did not support the clinical syndrome in the other two.

3. *Anginal Syndrome:* This symptom complex occurred in all of the 39 cases. Its importance in the development of the changes in the hands is discussed later.

4. *Radiation of Anginal Pain:* The site of radiation of the anginal pain did have some definite relationship to the development of *shoulder pains* and stiffness. The hand changes were bilateral and constant and there was *no* correlation between the site of radiation of the anginal pain and the development of the *hand changes.*

5. *Interval Between Infarction and "Joint Symptoms":* Minimum time interval was three weeks, maximum time interval 16 weeks. The time interval seemed to have no relation to the severity of the changes in the hands.

6. *"Joint" First Affected:*

	Cases		Cases
Both shoulders	9	Both hands	9
Left shoulder	8	Left hand	0
Right shoulder	10	Right hand	2
		Not known	1

The shoulder was the first "joint" involved in 27 patients. Such a high incidence of initial shoulder pain has been noted by others and has been attributed to a "periarthritis."

7. *The Distribution of Pain (early status)*: Pain occurred in both hands in 38 of the 39 cases. (Case 21 was observed only during the first two weeks of the nine weeks before sudden death.) Thirty-four patients had pain in one or both shoulders; five had pains in "other joints." Four of these had hypertrophic arthritis changes in the "other joints" involved.

The data show the frequency of the pain in the hands in this syndrome, pain being definitely present in all but one, in whom its absence was not determined.

The relation of the radiation of anginal pain to the appearance of early shoulder pain follows:

Radiation of Anginal Pain		Early Shoulder Pain	
To both upper extremities................	15	Both shoulders......... Left shoulder only....... Right shoulder only...... No shoulder pain........	11 2 1 1
To left upper extremity only..............	11	Left shoulder only....... Both shoulders.........	10 1
To right upper extremity only............	4	Both shoulders......... Right shoulder only	2 2
No radiation to upper extremities..........	9	No shoulder pain....... Both shoulders......... Right shoulder.......... Left shoulder	4 3 1 1

See discussion of the probable relationship of the radiation of anginal pain to shoulder pain and disability under heading of "periarthritis."

8. *Previous Rheumatic History*: Ten patients had a previous rheumatic history, four of whom had rheumatic fever in childhood. Four patients had hypertrophic arthritis, two had "rheumatism" of the right knee, one had rheumatism of the right foot and one had had "St. Vitus Dance." One patient had had both hypertrophic arthritis and rheumatic fever. No history could be obtained in any of our cases of "preëxisting arthritis" in the shoulders. In this series no change in preëxisting joint symptoms or deformities occurred as a result of the infarctions.

9. *Present Status (when last seen)*:

Atrophy of Hands: All but four patients showed atrophy of a discernible degree. Eighteen showed one plus atrophy, 10 had two plus atrophy, five had three plus and one four plus atrophy, and in one patient the degree of atrophy was not determined. Atrophy is a predominant feature in the later stages of the syndrome.

Limitation of Motion in Hands: All but two patients had limitation of

motion of the fingers of varying degrees; one patient had no limitation of motion; 17 patients had one plus; 12 had two plus; six had three plus; two had four plus and in one the degree of limitation was not determined. Limitation of motion is a predominant feature in the later stages of the syndrome.

Contracture of Palmar Fascia: Sixteen patients had no contracture, 13 had one plus contracture, eight had two plus contracture, one had three plus contracture.

Stiffness of Shoulders: Seventeen patients had no residual stiffness of the shoulders; 22 patients had residual stiffness of the shoulders. .

CASE REPORTS

Case 4. M. J. C., female, aged 63, housewife. There was nothing relevant in the past history or in the family history except that one sister had atrophic arthritis.

Present Illness: On April 27, 1939 the patient had a severe attack, characterized by precordial pain which radiated to the right shoulder and lasted for fifty minutes, and was accompanied by orthopnea, nausea and vomiting, and shock. She was admitted

Fig. 1. *Case 4:* Illustrating the claw-like appearance of the hands in a late stage. Dorsal view shows prominence of joints due to atrophy of soft tissues of phalanges and the tight stretching of the skin over the underlying structures. Skin appears glossy and transverse wrinkles have disappeared. Palmar view shows absence of ulnar deviation of the wrist; a contraction of palmar fascia and the maximum possible extension of the fingers.

to the hospital on the third day. Pulse rate was 100 to 120, weak and irregular. There was Cheyne-Stokes' respiration. Blood pressure was 70 mm. Hg systolic and 50 mm. diastolic. A pericardial friction rub was present. There was moderate pitting edema of the ankles, and there were râles at both lung bases. The extremities showed no evidence of muscle, nerve, bone or joint disease. Urine showed two plus albumin;
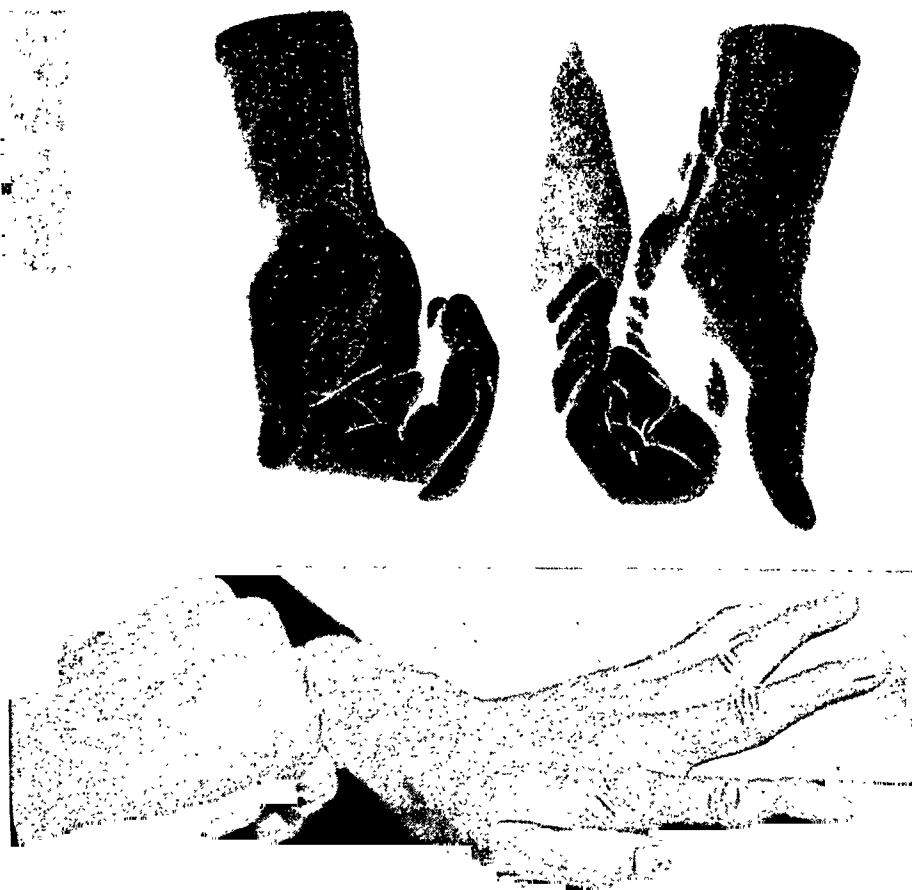
FIG. 2. *Case 7:* Lateral view shows maximum possible flexion of the fingers. Dorsal view shows subluxations resulting from violent efforts to achieve full extension of the fingers; no effusion or fusiform swelling of the joints and no ulnar deviation of the wrist. Skin appears tightly applied to the phalanges and atrophic and bronzed over the dorsum of the hand.

leukocytes 15,400, 74 per cent polymorphonuclears. Electrocardiogram is shown in figure 7. A critical period of oliguria, vomiting and shock lasted 10 days. She was discharged from the hospital on May 25, to continue her convalescence at home.

One week later she complained of pain and stiffness in the right shoulder, but the left shoulder and both elbows and wrists were asymptomatic. Three weeks later the hands began to feel numb and unwieldy and difficulty in movement of the fingers developed. The hands were held semiflexed. There was a uniform swelling without pitting edema extending to the finger tips. The skin appeared glossy and erythematous; and normal markings, particularly the transverse wrinkles over the dorsal phalangeal joints, were indistinct. The right shoulder was unchanged from the previous examination and function was normal in the left shoulder and both elbows and wrists.

Her cardiac status remained precarious; another myocardial infarction occurred on August 22, 1939, and anginal attacks occurred in spite of restricted activity. Pain and stiffness of the right shoulder persisted and the hands became gradually worse. She made no real effort to maintain motion as did the others whose eventual crippling was less (cases 7, 9, 19), and with time the flexion deformity in the fingers became fixed and permanent (figure 5). The palmar fascia was markedly contracted. Stiffness and disability of the fingers became her chief complaint, although mild angina persisted.

Examination on April 21, 1941 revealed entirely normal function of the left shoulder. The right arm could be raised above the head but not as far as the left, and

FIG. 3. *Case 9:* Lateral view shows maximum attainable extension in a late stage after much physiotherapy in an elderly patient. Dorsal view shows the glossy tightly applied skin over the fingers, and the false appearance of enlargement of the inter-phalangeal joints due to atrophy of the soft tissue of the phalanges.

abduction and rotation were not far from normal. The elbows and wrists were entirely asymptomatic and their function normal, as they had been throughout the entire course of her illness. The hands showed symmetrical anatomical and functional changes. Neither full flexion nor extension of the fingers was possible. The hands appeared claw-like and nearly immobile. Flexion deformity was most marked in the little and ring fingers. The skin no longer showed the uniform erythema; it felt thickened, seemed to be attached to the subcutaneous tissue and stretched over the bones. The palmar fascia was markedly contracted. Neither subcutaneous nodules nor Heberden's nodes were present. The joints, especially the distal joints,

were more or less fixed, but no crepitation or effusion was present (figure 5). The joints stood out because of atrophy of the soft tissues of the phalanges. The appearance of the hands was the same in May 1942 (figure 1).

This case illustrates the extreme deformities possible after myocardial infarction. The patient had had no "rheumatism" previous to this incident.

Case 7. L. B. G., male, aged 48, a rancher, had had known cardiac enlargement and mild hypertension since 1935. He was seen at his ranch home on May 22, 1940,
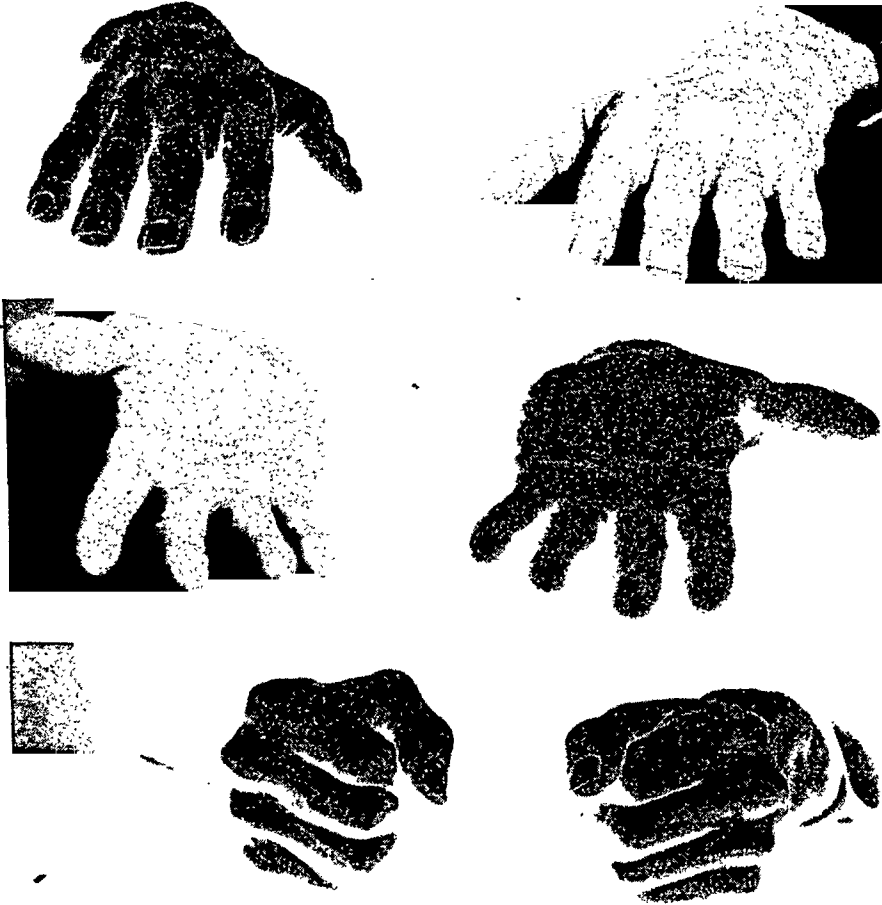
FIG. 4. Case 13: Dorsal view shows atrophy of soft tissues of phalanges and dorsum of hand, and prominence of phalangeal joints due to soft tissue shrinkage. Palmar view shows maximum extension of the fingers and moderate palmar fascia contraction. Fist-view indicates maximum possible flexion. Note that the middle row of phalanges makes an obtuse angle with the proximal row.

in a state of collapse, complaining of severe crushing pain in the precordium, with radiation to the left arm. He was admitted to hospital in a critical state, with pulse rate of 64, heart tones of extremely poor quality, and blood pressure of 140 mm. Hg systolic and 90 mm. diastolic. Leukocytes numbered 18,000, with 93 per cent polymorphonuclears, and temperature was 103° F. on the third day. On June 4, a paroxysmal ventricular tachycardia developed (serial electrocardiogram, figure 7). Following recovery from this episode there was gradual improvement. He was dismissed on June 28, to continue convalescence at home; there were no joint symptoms at this time.

Five weeks later he developed stiffness and pain in the shoulders, especially the left, and in both hands. Examination on August 27, 1940 showed limitation of motion, particularly in abduction, in both shoulders, more marked in the left than the right. There was no pain or limitation of motion in the elbows or wrists. The hands, especially the fingers, were uniformly swollen. The skin appeared tense and erythematous, but no pitting edema was present. The fingers were held slightly flexed and movement was greatly limited in all the phalangeal joints. Pain was severe with passive motion. No effusion or crepitation was present. No subluxation of the phalangeal joints was present.
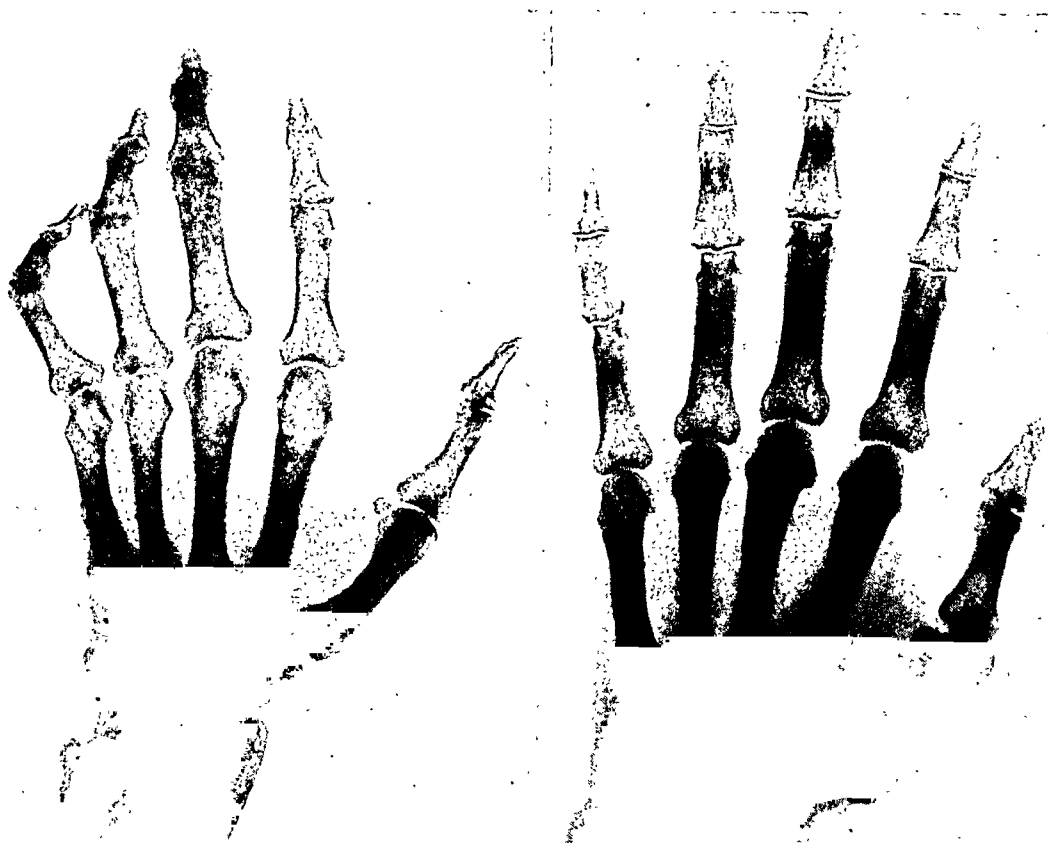
FIG. 5. *Case 4:* (*Left*) Claw-like fixation of the fingers renders it difficult to demonstrate that the inter-phalangeal surfaces are smooth and that there is no obliteration of the joint spaces. No proliferation of bone. Atrophy of bone is apparent.
Case 7: (*Right*) Marked decalcification. No proliferation, no increase or obliteration of joint space or other changes commonly seen in arthritis despite the fact that subluxations of the distal phalanges were present.

Two months later the condition and appearance of the hands had changed; the skin had lost its erythematous color, was less glossy, and felt thickened and seemed attached to the underlying structure. The patient had made strenuous efforts to regain full extension of his fingers, and a beginning subluxation of several of the distal phalanges had developed. A mild Dupuytren's contracture was present. There was no ulnar deviation of the hand. There were no subcutaneous nodes or nodules, and no joint crepitation or effusion. The fingers could be fully extended where subluxation had occurred, but flexion was incomplete (figures 2 and 5).

The severity of this man's infarction and the degree of change in the hands were about in the same proportion. He was the only patient who made violent efforts to

overcome his limitation of motion and who developed any subluxations of the phalanges.

Case 9. J. A. M., male, aged 68, clergyman. There was nothing relevant in family or past histories.

Present Illness. On June 15, 1937 an attack of severe precordial pain lasted two hours, radiating to both shoulders. On admission the patient was apprehensive. There was marked dyspnea; pulse was 90, regular; there was a blowing systolic apical murmur transmitted to the axilla; blood pressure was 170 mm. Hg systolic and 110 mm. diastolic. The extremities showed no evidence of muscle, nerve or bone
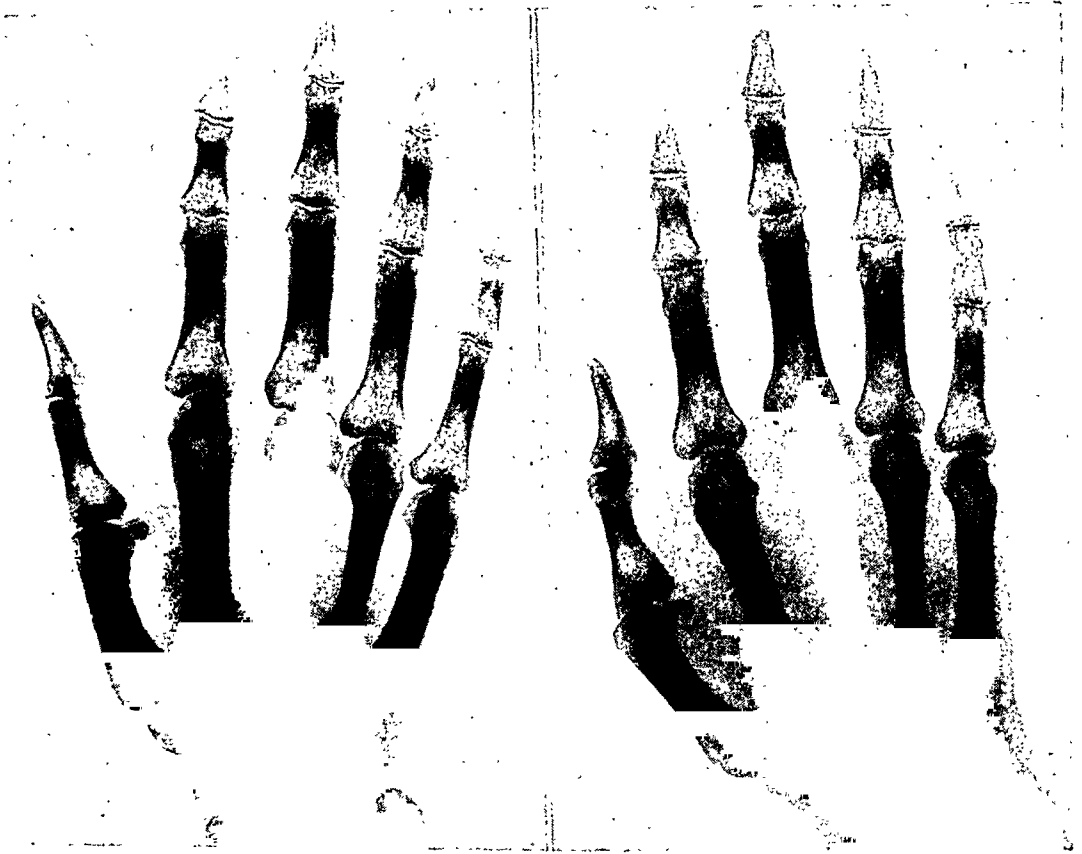
FIG. 6. *Case 9: (Left)* Very little joint space change for an elderly patient. Marked arteriosclerosis of the vessels of the hands as indicated by calcium shadow between second and third metacarpals.

Case 13: (Right) Decalcification of the phalanges, no changes in the wrist and very little change in the articulating surfaces of the phalanges.

or joint disease. There was no oral or dental sepsis, nor were there any signs of prostatic infection. Recovery was slow. Electrocardiogram is shown in figure 7.

Eight weeks after the attack stiffness of the right shoulder joint was followed by pain and stiffness in the left shoulder and in both hands. The shoulders showed limitation of motion. Elbows and wrists were normal and asymptomatic. The hands, and especially the fingers, showed swelling without pitting and a reddish cyanosis. The skin appeared tense, and the normal wrinkles of the hands and fingers were almost obliterated, both on the palmar and dorsal surfaces. The fingers were more comfortable semiflexed and painful if manipulated. There were no tender nodes or nodules, and no joint effusion or crepitation.

Four months later the erythematous swelling of the skin of the hands had disappeared, and the fingers were stiffened and felt wooden. The skin was thickened and gave the impression of being shrunken over the bones and somewhat fixed to the subcutaneous tissue; the interossei muscles showed atrophy; the phalangeal joints appeared enlarged as a result of the atrophy of the soft tissues of the phalanges. There was no crepitation or effusion in the joints (figure 6). Neither full flexion nor full extension could be accomplished, flexion being more limited than extension (figure 3).

This case showed early extreme vasomotor changes in the hands. Marked arteriosclerosis of the vessels of the hands may have been a factor in the persistence

CASE 7			CASE 13			CASE 4	CASE 9
5/22/40	6/10/40	6/12/40	6/26/40	6/27/40	7/5/40	4/29/30	6/20/37
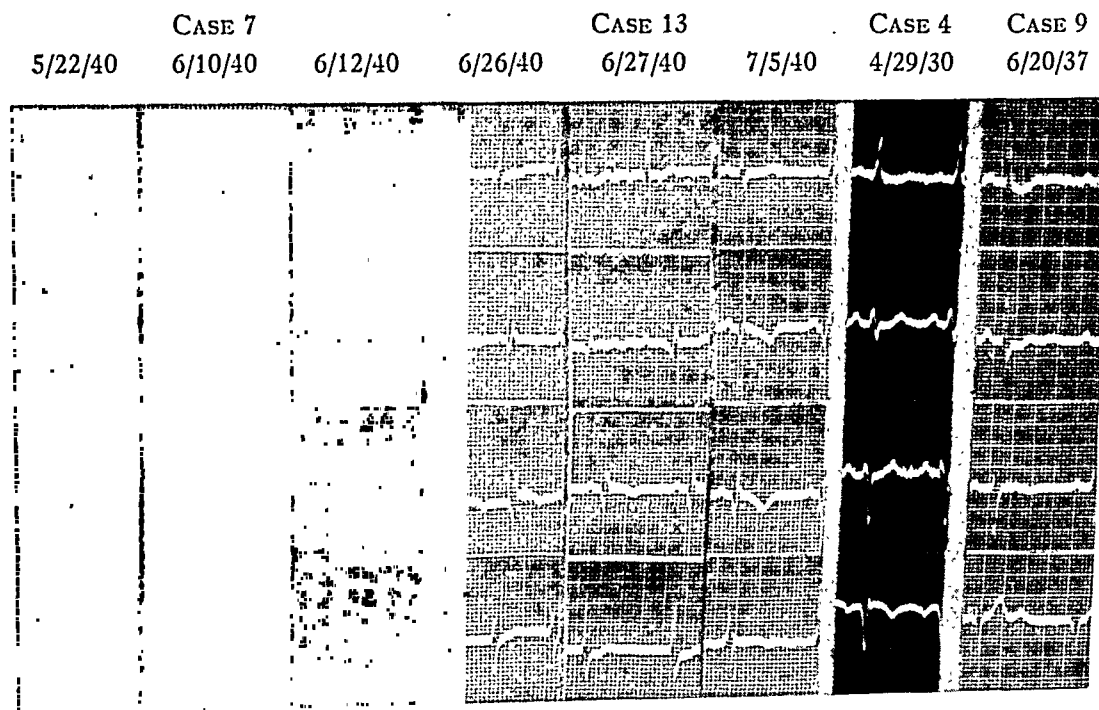
FIG. 7. Tracings from the four cases reported in detail.*

Case 7, 5/22/40. Changes compatible with acute myocardial infarction; anterior location; no digitalis. 6/10/40. Paroxysmal ventricular tachycardia (on longer tracing ventricular rate is found to be more rapid than auricular rate, ratio 5:3). 6/12/40. Further changes compatible with recent acute infarction, anterior location.

Case 13, 6/26/40. Compatible with acute infarction; no digitalis. 6/27/40. Transient fibrillation and flutter occurring while tracing was being made. 7/5/40. Further changes diagnostic of acute myocardial infarction, posterior location; no digitalis.

Case 4, 4/29/39. Compatible with recent anterior infarction.
Case 9, 6/20/37. Compatible with myocardial infarction, anterior location.
* Chest lead is Standard American Heart Association IV F.

of the changes (figure 6). Two years after the attack the hands were about the same. Restriction in flexion was marked, and when his hand was grasped it felt stiff and wooden.

Case 13. C. B., male, merchant. There was nothing relevant in his uneventful past history. A mild angina became gradually worse until June 26, 1940. He was admitted to the hospital on account of agonizing pain in the left chest which radiated to the left arm and the left side of the neck and was unrelieved by nitrites. There was marked dyspnea and fear of impending death. Leukocytes reached 20,000 with 84 per cent polymorphonuclears in 48 hours. Heart sounds were enfeebled. There was moderate enlargement, with no murmurs or irregularity. Blood pressure was 132

mm. Hg systolic and 100 mm. diastolic. There was no evidence of muscle, nerve, bone or joint disease. Tonsils were normal appearing and atrophic. There was no oral sepsis.

The patient's condition remained precarious for many weeks, with many attacks of angina decubitus. Transient auricular fibrillation developed on several occasions throughout his long hospitalization (serial electrocardiogram, figure 7).

No symptoms were noted in the joints until July 27, 1940, when he complained of stiffness and pain in his left shoulder. Three weeks later he noticed stiffness and pains in the fingers. Examination showed a uniform swelling of the hands and fingers without pitting. The skin showed a reddish cyanosis, and the normal wrinkles had disappeared. The fingers were held semiflexed and any movement, either passive or active, was associated with pain. His hands remained unchanged for many weeks, subjectively and objectively. At no time during his long hospitalization did he have pains in the elbows or wrists. By October 1940 the hands had changed considerably. The skin, which previously had been erythematous, now showed brownish pigment. Some of the glossiness and the "ironed out" appearance had disappeared. Difficulty was experienced in lifting the skin from the subcutaneous tissues. The interjoint spaces were shrunken, and the tendons appeared prominently on the dorsal and palmar surfaces. Movement of the fingers was greatly limited so that he was unable to move them much from a semiflexed position. There were no Heberden's nodes or nodules, and no fluid or crepitation in the finger joints. A definite palmar fascia contracture was apparent.

Following discharge he remained crippled by angina occurring with mild physical effort or emotional upsets. Examination on October 7, 1941 revealed right shoulder normal, left shoulder slightly limited in motion, particularly in abduction. The hands and fingers showed no improvement in function or change in appearance (figures 4 and 6).

This man had many mild anginal attacks following the severe, near lethal, myocardial infarction, and fear was a prominent feature of all the attacks. He stated after the more severe anginal attacks "my hands feel worse." His deformities were severe, particularly the atrophy and limitation of motion and although his degree of arteriosclerosis did not approach that of case 9, the deformities and functional disturbance were about the same. He illustrates the rôle of repeated attacks of pain associated with fear in the development of the syndrome.

DISCUSSION

The incidence of disabling changes in the hands following myocardial infarction in this series is high, 39 patients or 21.8 per cent in 178 consecutive cases of myocardial infarction. We believe that it would be found to be as high or higher in any comparable series, were it not for certain factors: Some patients do not survive the initial infarction long enough to develop the syndrome (time in this series, three to 16 weeks); mild symptoms in the hands are so overshadowed by cardiac symptoms as not to be mentioned by the patient; the classifying of many cases of the type reported here as "rheumatoid" or "atrophic arthritis," and inability to obtain follow-up data on some cases.

Because of the frequency with which this syndrome follows myocardial infarction, its recognition may be important in substantiating the occurrence of a myocardial infarction in those patients in whom the electrocardiographic changes or clinical symptoms were not conclusive.

DIFFERENTIAL DIAGNOSIS

Rheumatoid Arthritis: The disabling changes in the hands following myocardial infarction are frequently mistaken for rheumatoid arthritis. Sharp contrasts in the clinical manifestations, however, make it obvious that this syndrome is not rheumatoid arthritis, but a distinct clinical entity which has the etiological, clinical, and morphologial criteria of sclerodactylia. It is probable that there are some etiological factors which are common to sclerodactylia and to some cases of rheumatoid arthritis. In both conditions the pathological changes are referred but not limited to the joints, that is, muscle, bone and fascia participate in the changes in the extremity. Joint involvement in rheumatoid arthritis may be strikingly symmetrical and bilateral, even though it is rarely limited to the hands, as is invariably the case in this syndrome. Studies of the nail beds which have been made in rheumatoid arthritis show fewer capillaries and capillaries of narrower caliber, not unlike the picture seen in sclerodactylia, and actually sympathectomy has been tried for symptomatic relief in both.

The most striking characteristic of this syndrome is uniformity. The mode of onset, clinical course, and the clinical manifestations follow a quite regular and uniform pattern. The changes which are limited to the hands are symmetrical and bilateral, and of approximately equal severity in the same individual.

In this syndrome the earliest changes occur in the skin of both hands. The skin appears edematous and glossy, and a feeling of tension and stiffness of the entire hand is complained of. In rheumatoid arthritis the skin does not show such consistent or uniform changes; tension occurs over one or more swollen joints. Instead of uniform discoloration of the skin which varies from pale violet to red, and is characteristic of this syndrome, in rheumatoid arthritis localized redness may occur only over the swollen joint itself. In this syndrome, the skin temperature is the same over the whole hand and not elevated, whereas in rheumatoid arthritis the temperature is often increased locally over an affected joint. The isolated fusiform swelling of the joint so typical in rheumatoid arthritis may exhibit extreme tenderness on lateral pressure, whereas the uniformly swollen fingers in this syndrome exhibit diffuse tenderness which is not especially localized to the joint. Although rheumatoid arthritis may involve several joints of the fingers simultaneously, the acuteness of the symptoms may be subsiding or stationary in one joint, at the same time that they are increasing in severity in an adjacent joint; by contrast in this syndrome, the acuteness of the symptoms is of more or less equal severity, bilaterally, and the progression or recession of symptoms is usually even and uniform in all the fingers. The stiffness in this syndrome involves the whole hand, and is not, as is often the case in rheumatoid arthritis, localized to a joint. Finally, in striking contrast to this syndrome, in rheumatoid arthritis, other joints such as the wrists, elbows and knees may be affected simultaneously with the hands. It is especially

in the early stage of this syndrome that the differential diagnosis presents difficulties, and then only if the rheumatoid arthritis is limited to both hands, which is uncommon.

Later, sharp deviations in the clinical course of the two conditions occur. In the syndrome the uniform swelling and discoloration of the skin gradually subside, the skin of the entire hand loses its elasticity and appears hard and leathery and uniformly attached to the underlying structures, stiffness rather than pain becomes more prominent, and the entire hand is held rigidly with the fingers semiflexed. In rheumatoid arthritis the skin appears parchment-like and tense over an isolated swollen joint in which effusion has occurred, so as to give the characteristic spindle-shaped finger; adjacent phalangeal joints of the same finger may appear normal and function well. Subluxations, so common in rheumatoid arthritis, occur rarely in this syndrome and only as a result of violent attempts to achieve extension of the fingers. Ulnar deviation and subcutaneous nodules so characteristic of rheumatoid arthritis do not occur. Contractions of the palmar aponeurosis of various degrees are common in the syndrome and unusual in rheumatoid arthritis.

Finally, the syndrome occurs usually after middle life in patients with severe cardiovascular disease and has a tendency to recession, in contrast to rheumatoid arthritis which begins usually before middle life in patients without cardiovascular disease, and has a strong tendency to progression and extension.

"Periarthritis": In the literature this term refers especially to the stiffness and pain in the shoulder which often follow myocardial infarction, and appeared in 74 per cent of 29 out of 39 patients in this series. We believe that the pain and stiffness in the shoulders and the syndrome of disabling changes in the hands are not related to one another even though they both follow myocardial infarction (paragraphs 6 and 7 under "Summary of data in table 1").

In this series of cases a preëxisting arthritis appeared to play no rôle, for none of the patients had symptoms referable to the shoulder joints previous to the infarction. The autopsy on case 21 (table 1) supports this view, as no gross or microscopic changes suggestive of an arthritis were found in the shoulder joint. Another point against the importance of "preëxisting arthritis," or "periarthritis," is the fact that elbows and wrists in this series showed no limitation of motion or pain.

It is not necessary to assume a "preëxisting arthritis" to account for the early shoulder pains and stiffness in the shoulders. The changes could be the result of an unconscious protective mechanism in which the patient holds the arm rigidly against the side of the chest to prevent recurrence of anginal pain. The fixed attitude of patients during an anginal attack is well known.

The important feature of the shoulder disability is the appearance of exquisitely tender areas about the shoulder joint and spine. Following myo-

cardial infarction tender areas may be noted in the skin, muscles, or other structures. The referred pain and tenderness were studied by MacKenzie, who felt that the stream of pain impulses from the heart in myocardial infarction altered the condition of the spinal gray matter ("irritable focus") so that impulses were sent to the corresponding segments of skin, body wall, etc., which accounted for tender areas in the skin (cutaneous hyperalgesia), tenderness in the muscles such as the trapezius and deltoid (muscular hyperalgesia) and tenderness over the first to fourth thoracic spines in diseases of the heart. Besides these sensory phenomena, motor effects such as painful contractions of corresponding groups of muscles like those of the shoulder girdle or intercostal muscles may also be produced[16] as a reflex response to the cardiac pain.

Suggestive support of this explanation of shoulder pain and stiffness may be found in the figures in paragraph 7 of the "Summary of data in table 1."

In conclusion, it is felt that the pain, stiffness, and limitation motion in the shoulder region develop because of voluntary or involuntary splinting of the joint on account of the fear of initiating recurrence of the anginal pain and because the shoulder itself is the site of reflex tenderness. The pain and the "tender points" are a peripheral reflex response to the anginal pain comparable to the pain and the tender point below the right scapula so often noted in gall-bladder disease. The shoulder symptoms are not considered to be related to the hand changes or to share in the chief etiologic factor of the hand changes, viz., ischemia produced chiefly by vasoconstriction of the arteries of the hands.

THEORETICAL CONSIDERATIONS

Certain anatomical and physiological considerations[16] make it appear reasonable to explain the disabling changes in the hands following myocardial infarction as due to nutritional disturbances (chiefly anoxia) resulting from local ischemia (vasoconstriction) and anoxemia in the hands and fingers. It does not appear necessary to assume the presence of a "preexisting arthritis" or a gouty diathesis as other writers[9, 10, 11] have done.

These changes in the hands and fingers have been compared with the sclerodactylia of Raynaud's disease because of certain similarities in etiology, appearance and clinical course. The condition does not progress to the extremes of gangrene and trophic ulcers of the fingers as it does in some cases of Raynaud's disease, because one important mechanism, the vasoconstriction resulting from the cardiac pain, is relatively temporary and intermittent.

The limitation of the syndrome to the hands, to the exclusion of the elbows and wrists and other "joints" of the body (except for the shoulders which have been dealt with earlier), places the etiology on an anatomical basis, in which a local ischemia resulting from impaired function of the peripheral arteries of the hands is the localizing factor.

It is felt that the factors which are etiologic in the production of the local changes in the hands and fingers are:

1. Vasoconstriction of the peripheral arteries of the hands resulting from the cardiac pain.
2. Preëxisting arteriosclerotic narrowing of the vessels of the hands.
3. Anoxemia of varying duration and intensity resulting from the myocardial infarction.

Discussion of these three factors, all of which contribute to a state of anoxia of the tissues of the fingers, follows:

1. The Effects of the Vasoconstriction Caused by Pain: These are of the greatest importance in the development of the disabling changes in the hands following myocardial infarction. The pain here is regarded as occurring with either "spasm" or closure of coronary vessels. The changes in the hands do not develop where simple anginal attacks have not been interspersed with or followed by cardiac infarction. The infarction would appear to have a two-fold effect in producing changes in the hands. The greater effect is due to (a) reflex vasoconstriction of the peripheral arteries produced by the pain of the coronary closure which far exceeds the pain of simple anginal attacks in duration and intensity, and (b) vasoconstriction produced by the release of adrenalin as a result of fear or pain.

The nerve paths between the heart and hand have long been studied.[15] The pain impulses originate in the heart and pass by the sensory nerve fibers chiefly to the eighth cervical and the upper four thoracic nerve roots of the spinal cord. From here the pain is most often referred down the inside of the arms (Thoracic 1), and to the sides of the chest (Thoracic 1, 2, 3).[15] Rami from these segments of the cord connect with the lower cervical and upper thoracic sympathetic ganglia which furnished vasoconstrictor fibers to the upper extremity.

In connection with the distal vasoconstrictor effects of cardiac pain, it is important to recall that both the phenomena of Raynaud's disease and severe anginal pain may be relieved by cervicothoracic ganglionectomies. The importance of the nervous pathway between the heart and the hands is further emphasized by the demonstration that ice cubes held in the hands will lower "exertion tolerance" in cases with angina pectoris.[13]

It has been shown that the failure of cervicothoracic ganglionectomy in Raynaud's disease can be explained by the fact that there can be secreted a sufficient amount of adrenalin in response to emotions resulting from pain and fear to produce peripheral vasoconstriction. This indicates the importance of emotions, such as fear, in producing vasoconstriction of the peripheral arteries and *fear* is a prominent feature in the pain of coronary closure.

Hence, the anginal or occlusion pain may produce vasoconstriction of

the peripheral arteries directly through the cord (reflex arc) or indirectly through the higher centers (adrenal stimulation).

2. The Effects of Preëxisting Arteriosclerotic Narrowing of the Arteries of the Hands: Since occlusive vascular disorders are far more common in the lower extremities in general arteriosclerosis, it is evident that the presence of arteriosclerosis is of minor importance in the development of these changes in the hands; it merely makes a small, but perhaps often determining addition to the sum total of ischemia and nutritional deficiency. The chief determining factor remains the pain and its sequel of vasoconstriction.

3. The Effects of Anoxemia of Varying Duration and Intensity Resulting from the Myocardial Infarction: For the reasons outlined above it is believed that by far the most important effect of the myocardial infarction in the development of the changes in the hands is the increased vasoconstriction from pain and fear. However, it seems probable that during the acute phase of the infarction the lowered oxygen content of the blood, and possibly actual toxic substances liberated by the death of the cardiac muscle, add to the sum total of the nutritional deficiency in the hands. Obviously the anoxemia resulting from lowered blood pressure and lessened cardiac output during the acute phase of the infarction is *not alone sufficient to produce* damaging changes in the hands or these changes would appear in the feet also. Yet, it is reasonable to suppose that an often prolonged and quite intense anoxemia adds to the nutritional disturbance and tissue anoxia in hands which are being subjected to severe vasoconstriction, and may be a determining factor in the development of the syndrome.

COMMENT

Up to 1940, by which time 17 of our 39 cases had been collected, we had found no reports in the literature of the disabling changes in the hands following coronary thrombosis or myocardial infarction such as those described in this paper. Shoulder pain following myocardial infarction had received considerable attention.[4, 5, 6, 7, 9] In these reports the painful condition of the shoulder is often referred to as a "periarthritis," and it is suggested that the shoulder disability may result from referred anginal pain and from voluntary or involuntary splinting of the shoulder. Several writers suggest that painful shoulders may warrant the suspicion that a myocardial infarction has occurred a short time before.

Ernstene and Kinell[9] note changes in the hands in several of their 17 cases of post-infarction shoulder pain reported in 1940. The "Remarks" for two of their cases indicate that the authors had observed changes in the hands very much like those reported in our series; their case 10 suggests the early stage of the syndrome, and case 12 resembles a later and more fully developed stage with characteristic involvement of the fingers, which these authors regard as changes due to "rheumatoid arthritis" involving the fingers.

The substance of Askey's important contribution,[10] published in 1941, was brought to our attention by a personal communication * in the spring of 1940. Askey describes "the syndrome of combined shoulder and hand disability" developing in 18 cases of cardiac infarction and four cases of longstanding angina pectoris. He describes clearly the changes in the hands that are the subject of this report, and observed thickening of the palmar aponeurosis in seven of his cases. Although he remarks that "two cases suggested that the rôle of the sympathetic nerves was predominant," he feels that "the more common type suggests merely a rather rapid development of arthritis"; he considers the hand involvement to be an extension of the syndrome of shoulder pain described by earlier writers, and places a "preëxisting arthritis" or "latent arthritis" in an important etiologic rôle. However, he gives a "sympathetic nerve disturbance" an important place in the etiology even though he does not identify the changes in the hands with the sclerodactylia encountered in certain cases of Raynaud's disease. He states that "the course of the hand disability was characteristic of neither longstanding rheumatoid arthritis nor osteo-arthritis."

In spite of some differences in the observations and in the explanations given for the development of the changes observed, Askey's observations and those reported in this paper, pursued independently and simultaneously, appear to establish these changes in the hands following myocardial infarction as a definite syndrome.

The recognition of the syndrome is becoming more frequent, as indicated by Meyer and Binswanger's [12] recent report of three cases with changes in the hands similar to those which are the subject of this paper.

SUMMARY

1. A syndrome characterized by disabling changes in the hands, which closely resembles descriptions of sclerodactylia, may develop following myocardial infarction. The syndrome developed in 39 (21 per cent) of a series of 178 consecutive cases of acute myocardial infarction.

2. The clinical observations on the 39 cases are presented in tabular form. Four cases are reported in detail with photographs, roentgenograms of the hands, and electrocardiograms.

3. The term "post-infarction sclerodactylia" is offered as a convenient and rational name for this syndrome.

4. It is suggested that many cases showing this syndrome are at the present time classified as "rheumatoid arthritis," "atrophic arthritis," "atypical arthritis," "causalgia," etc.

5. It is suggested that the etiology of "post-infarction sclerodactylia" is anoxia of the tissues of the fingers, produced chiefly by ischemia resulting from reflex vasoconstriction of the arteries of the hand induced by cardiac pain; and that the lesser ischemic effects of arteriosclerosis of these arteries

* To Dr. F. R. Schemm, whose encouragement and interest were helpful during this study.

and the local anoxemia of the fingers which is part of the general anoxemia resulting from myocardial injury may increase the degree of the damaging tissue anoxia.

Addendum: Since this article was proofread Kehl [16] has reported six cases encountered by him of Dupuytren's contracture occurring after myocardial infarction, and he quotes Hale Powers as explaining the palmar phenomenon on the basis of irritation of the sympathetics and places it "in the same category as pulmonary hypertrophic osteoarthropathy, *scleroderma* and other trophic disturbances."

BIBLIOGRAPHY

1. Craig, W. McK., and Horton, B. T.: Diagnosis and treatment of vascular disorders of the extremities, Surg. Clin. N. Am., 1938, W. B. Saunders, Philadelphia.
2. Longcope, W. T.: Scleroderma, Oxford Medicine, 1934, vi, 828 (6).
3. Barker, L. F.: Diseases of the sympathetic system: scleroderma, Monographic Medicine, 1916, D. Appleton-Century, New York, vi, p. 1077.
4. Howard, T.: Cardiac pain and periarthritis of the shoulder, Med. Jr. and Rec., 1930, cxxxi, 364-365.
5. Edeiken, J., and Wolferth, C. C.: Persistent pain in shoulder region following myocardial infarction, Am. Jr. Med. Sci., 1936, cxci, 201.
6. Boas, E. P., and Levy, H.: Extracardiac determination of site and radiation of pain in angina pectoris with special reference to shoulder pain, Am. Heart Jr., 1937, xiv, 540.
7. Leech, C. B.: Painful shoulder in association with coronary artery disease, Rhode Island Med. Jr., 1938, xxi, 104-106.
8. Spillane, J. D., and White, P. D.: Atypical pain in angina pectoris and myocardial infarction, Brit. Heart Jr., 1940, ii, 123-131.
9. Ernstene, A. C., and Kinell, J.: Shoulder pain as a sequel to myocardial infarction, Arch. Int. Med., 1940, lxvi, 800.
10. Askey, J. M.: Personal communication, 1940.
11. Askey, J. M.: The syndrome of painful disability of the shoulder and hand complicating coronary occlusion, Am. Heart Jr., 1941, xxii, 1-12.
12. Meyer, J. C., and Binswanger, H. F.: Recent myocardial infarction followed by involvement of the joints of the hand and wrist, Am. Heart Jr., 1942, xxiii, 715-719.
13. Freedberg, A. S., Spiegel, E. D., and Riseman, J. F.: Studies on the effect of cold and heat in patients with angina pectoris, Jr. Clin. Invest., 1941, xx, 4.
14. Pemberton, R., and Osgood, R. B.: The medical and orthopedic management of chronic arthritis, 1934, The Macmillan Co., New York.
15. Wright, S.: Applied physiology, 1934, Oxford Medical Publications, New York.
16. Kehl, Kenneth C.: Dupuytren's contracture as a sequel to coronary artery disease and myocardial infarction, Ann. Int. Med., 1943, xxix, 213-223.

ADJUSTMENT IN WARTIME *

By Edward L. Bortz, Commander MC–V(S) USNR, F.A.C.P.,
Philadelphia, Pennsylvania

A Nation Challenged

When a peace loving nation is attacked, its citizens are called upon to make the most important adjustment of a lifetime. In total war, everyone is an important cog in his country's defense. Considerations of individual convenience and safety must be subordinated for national security. In time of peace, the various vocations and avocations offer the citizen a wide choice of useful pursuits, and independence of individual action is a sign of national vitality. However, when face to face with a national emergency, a rigorous discipline is essential to efficient military action. The energies and lives of millions must be forged into a military instrument of sufficient power to meet the invaders' challenge.

Therefore, far-reaching adjustments of an individual and national character are essential if the nation is to survive.

Defining Objectives

A clear understanding of the ideals that draw a nation into war is a powerful and necessary stimulant for all. Conflicting views of the national aim and violent disputes in the economic, business, political, and professional spheres dissipate a nation's military driving power. A house divided against itself can not stand.

In the present World War, the goal to be attained can be clearly crystallized. Indeed, it must be crystallized and kept forcefully before all of the citizens to serve as a catalyst for their continued participation in the war effort.

The Atlantic Charter is a significant document in its definition of the objectives for which the United Nations are fighting. The four freedoms as outlined in the Charter are:

1. Freedom of speech and expression.
2. Freedom of worship.
3. Freedom from want, which, translated into world terms, means equal understanding which will secure to every nation a healthy peacetime life for its inhabitants.
4. Freedom from fear, which means a reduction in armament to such a point and in such a fashion that no nation would be in a position to commit an act of aggression against any neighbor.

These, in simple terms, define our goal, winning the approbation and participation of free men everywhere.

The doctrine of a master race, which has been a leading political and social ideal in the Prussian state since 1807 and which gradually has subordinated the more peace-loving elements of the German state, has no respect for the ideal of freedom which is the central core of our country's national existence. That the Germans have a right to their own views of national policy can not be denied; that the rest of the more than two billion people inhabiting the earth will subordinate themselves to the German will, is for the present conflict to establish. In adjusting to war, it is essential to keep objectives in the forefront.

· SOURCES OF NATION'S POWER

Near the close of the Civil War, Henry Thoreau pointed out that, as a nation, we had about exhausted our inherited liberty, and that the stock of passively acquired freedom was running low. Thoreau indicated that new obligations were appearing for the American citizen.

The vast extent of our nation's natural resources, development of which has brought new visions of culture and enjoyment, gives us a justified sense of pride and a certain feeling of security for the future. However, as Napoleon [1] pointed out "war is three-fourths a matter of morale; physical force and material make up the remaining one-fourth." Material is of secondary importance except in the hands of a military force emotionally stirred to great action with a religious fervor that will not fail. The pioneer spirit that brought to our shores the restless explorers of earlier days has nurtured a type of citizen with a genius for invention and utilization of resources which constitute our nation's principal heritage.

EFFECTIVE MOBILIZATION

Effective mobilization requires adequate adjustment on the part of every man, woman, and child in the direction of national defense. It requires a strict evaluation of abilities and limitations so that each unit of the population may be gainfully employed. The willingness of the citizen to place himself unreservedly at the service of his country is a direct measure of his patriotism, his interest in his nation's survival.

Morale is a fighting force which sustains men, women, and children under all types of strain. It is necessary for success in any civilian enterprise but has a life and death value in the soldier. Morale, as a fighting force, has been demonstrated by the British who lived through day to day stresses of total war.

Personnel Selection: Although the nation's manpower is, on the whole, a healthy body, misfits must be promptly screened out as a preliminary to vigorous military discipline.

Rowntree [2] has revealed that 25 per cent of the 18 and 19 year olds ex-

amined under Selective Service were found unfit for military duty in spite of the fact that they are regarded as the healthiest group in the nation. Although the major cause for rejection was eyesight which accounted for 4.5 per cent, other major causes were mental, 2.8; musculo-skeletal, 2.3; cardiovascular, 2, and educational deficiencies, 1.9.

Thom [3] points out that of three and one-half million men examined in mobilization centers, 69,394 were rejected because of some mental aberration. The frequency of neuroses in this group reported by Thom was as follows:

1. Neurasthenia.
2. Conversion hysteria.
3. Anxiety states.
4. Psychoses.

There is no place in military action for the unfit, the defectives, the alcoholics, the syphilitics, and similar invalids. Minor physical disabilities, although disqualifying the individual from participating in military maneuvers, are no handicap for one of sound mind who is eager to be a contributing factor rather than a consumer in the nation's war effort. Scientific selection and the proper placing of men is important to avoid the development of a large-scale liability.

Even before the outbreak of the present war, the psychiatrists of our nation developed a workable prophylactic approach for the selection of candidates for the armed forces. Transfer from the free and easy civilian way of life to a strict military régime subjects individuals to certain stresses and strain. Tests have been devised whereby the stamina of the embryo soldier may be fairly satisfactorily evaluated.

Menaces to Morale: Following a review of the casualties of the first World War, Lord Horder made the statement that "war produces no new nervous disorders." The term shell-shock, so popular 20 years ago as a catch-all for innumerable forms of nervous instability, has been wisely discarded. In reality, many of these are instances of an anxiety state with histrionic demonstrations as a means of escape.

There has been an exaggerated estimate of the tendency of war to produce nervous breakdown in healthy individuals. Osler [4] pointed out that "there are some people who will never be able to stand up by themselves." It has been estimated by various observers, including Strecker, [5] that approximately 10 per cent of those eligible for military service do not have the "fighting heart." Their inabilities, however, should be identified in order that these individuals may contribute to the national effort. Someone has pointed out that the worst fighting men are often the best diggers and in the latter capacity they will be helpful in a routine way. Likewise, these men find pride in wearing the uniform and are happy in the presence of friends on their own level. Disciplinary problems in the not-so-bright men are said to be almost entirely nil.

• The neurotic tendency of men can be ordinarily controlled when they are doing suitable work, and in this way those who are misfits may attain a position of usefulness elsewhere.

The inheritance of defective genes and the environmental ill effects of broken homes have created large numbers of unstable individuals. In a recent book Gillespie[4] has pointed out that the "earliest cultural factor, the family, is of great significance in the genesis of a psychoneurosis." Furthermore, he states that "the main preventive of neurosis in doctors and in professional men generally might be summed up in the phrase 'professional attitude.' The individual identifies himself with his job which becomes a pivotal value for him."

The principal menace to morale is probably ignorance of what we are fighting for today. Apathy and lethargy, regarded by the medieval church as deadly sins, may be significant preceding either a psychoneurosis or an antisocial act. The Britons have frequently remarked "we would rather be bombed than bored." Isolation from congenial surroundings has opened the door for neurosis in susceptible persons. Gregariousness, as demonstrated by the Britons, has proved to be a substantial asset in maintaining morale. Idleness is a menace, and for the skilled or unskilled, work is a stabilizing factor. Gillespie[4] maintains that the more the individual is subjected to the will of the state, the greater is the liability to panic or apathy. This was confirmed recently by a German refugee who contrasted the strong inner discipline of the Britons with that of the Germans on whom discipline was imposed by authorities from without.

Separation anxiety studied by Fairbairn[6] is universally a factor of war neurosis. The occurrence of an exaggerated degree of dependence among neurotic soldiers is widespread, and Fairbairn[6] believes that the truth is not so much that the boy craves to go home because he is ill as that he becomes ill because he craves to go home. Fairbairn[6] maintains that it is impossible to draw any real distinction between war neuroses and homesickness.

Pegge[7] is of the opinion that some of the neuroses of war differ considerably from those of peace. The circumstances of war, being emotional stimuli of unwonted intensity and suddenness, cause a symptomatology more florid, more extreme, and more essentially abnormal than do the more moderate and slowly acting circumstances of peace-time life. This degree in difference of symptoms really becomes obvious only when weighed, in each case, against the personality before breakdown. To understand neurosis is to understand personality. Pegge[7] states that the process which, in the growing up of a child, leads to the development of a healthy independent adult leaves a trail of emotional events and conflicts overcome, to the more difficult of which there may be a regressive return in times of great stress. Indeed, retrogression itself can not be considered as a pathological mechanism since it may be a signal of distress and, when promptly recognized, may be the means of saving the personality. Dependence as a mechanism may be useful

in adult life as it is in the child, but it needs be followed by a phase of wise weaning. It has been stated that the conflict, "infantile dependence" versus "adventuring into adult life," is present in everyone, normal and neurotic alike. Thus neurosis is merely a quantitative variation, at best a modification, rather than a contraindication of the normal.

Why do some soldiers break down in the face of danger whereas others do not? Fairbairn [6] states that the capacity to endure danger varies with the extent to which the individual has outgrown the stage of infantile dependence. This agrees with the notorious proneness to anxiety which characterized the child as compared with the mature adult. It is, of course, important to differentiate adolescent youngsters of 18 and 19 who have entered the service and may show certain tendencies to abnormal behavior. With wise guidance these problems are promptly cleared away.

Youthful soldiers with overprotective mothers, coming from homes in which they have been sheltered and their adolescent experiences prolonged, frequently appear as neurotic. If a lad has joined the service to escape parental discipline and finds the supervision is more strict than at home, he may develop a neurosis due to maladjustment.

Borderline cases are frequently known to family doctors, and the latter may be of assistance to the officers of induction centers in pointing out prospective soldiers who have personality disorders.

Menaces to Morale

1. Ignorance of objectives.
2. Ill health.
3. Inadequate diet.
4. Loss of sleep.
5. Continuous work without periods of rest and recreation.
6. A task for which one is unfitted.
7. Idleness.
8. Boredom.
9. Strange and new type of existence.
10. Depressing news from home, or hysterical relatives.
11. Arguments between important national groups.
12. Predisposition to neurosis.

Margins of Reserve: There is, of course, a limit to the stress and strain that anyone can stand without some evidence of temporary maladjustment. This varies with the individual and from time to time in the same person. Personality deficiencies are more likely to appear in an individual who is physically below par or who is fatigued.

The average young American is healthy in body and mind, with family and social assets which serve as useful supports in time of emergencies. Approval of family and associates in his course of action is stimulating support.

Conversely, parental reproof, lack of understanding, social castigation may reduce ability for adaptation. Many psychopathological symptoms appear as defense mechanisms as anxiety attendant upon infantile dependence.

The separation complex may affect not only the soldier, but his family as well. A clear understanding of the issues involved in global war with an appraisal of each individual's responsibilities as a citizen is an important ingredient of reserve store. The nation's margin of reserve in morale will determine its ability to survive.

Mechanisms of Adjustment: During the first World War the incidence of war neuroses varied between groups in inverse proportion to their morale. Even so-called normal soldiers may develop a transient war neurosis in circumstances in which morale has been sufficiently impaired demonstrating that emotional maturity is a matter of degree and is never absolute.

Since war is abhorrent to all, it must be presented in such a light as to allow every individual to mobilize aggressive urges in the service of the nation, as pointed out by Sillman.[8] Of importance is a profound knowledge of both social and psychological forces on the part of leaders responsible for indoctrination for war. There needs be a training of the emotions in order quickly to supply a motive force of sufficient strength to enable the soldier to face enemy fire. To persuade armies of men to work, and fight, and die effectively in destroying a vast enemy demands mature self control. Adjustment must be complete; educating Americans to the art of war must be approached with a clear understanding of the intricacies of personality and its deeper hidden reactions.

To adjust for participation in the war effort, the individual's loyalty to his nation must be intensified, and he must externalize his aggressiveness toward the enemy to complete willingness to sacrifice all if need be. There is a strong fascination for war and destruction in the Japanese mind and our enemies are kept stimulated by an overwhelming desire for world power. To combat this adequately and preserve the principles of democracy requires a very clear understanding and intense belief in those principles.

Despite America's belief in democracy Sillman[8] states that education as to its deeper meaning has been strangely lacking. In peace time, patriotism as a national attribute has not been kept in the foreground.

A condensation of many sentiments is necessary for an ideal to be intensely felt and acted upon. The more sentiments that can be centered into an idea, the stronger is that idea supported.

As pointed out by Sillman,[8] the strongest forces in the individual's personality to which democracy should appeal are religion and personal honesty. To intensify individual belief in it democracy should be related to these forces.

Democracy is derived largely from the biblical concept that every man has a soul equal before God. The high spiritual goal that an individual's impulses and ideals must be devoted to the welfare of others is derived mostly

from religious sources. It is concretely expressed in the Atlantic Charter. Furthermore, it represents a principle of national existence which is alien to the German and Japanese national minds.

Democracy needs be demonstrated as a desire to introduce spiritual values into political and social life. Without these high ideals, the tolerance and basic trust in the common man on which democracy is based could never have been developed, nor can it continue. Therefore, there needs be a clustering of religious and moral principles with democracy, in order to preserve a respect for individual life.

Furthermore, the benefits of scientific, intellectual and aesthetic creativity will be preserved in the democratic principle of freedom for which our nations stand committed to total war. In the Nazi and Japanese society there is an utter disrespect for the individual and, therefore, creative work is impossible.

A second method for intensifying loyalty is through projection and introjection. Few people can sustain beliefs or intense loyalty without external reinforcement. This mechanism can be called into play by impressing on the individual the feeling that every one is concerned with this idea and the intensity of his loyalty. The individual must be brought to realize that he is a significant link in a chain and an integral part of an important undertaking. He needs to regard himself as an example for all others. The only way of combating the terror of being isolated and overwhelmed by the vast power of the enemy is by having the nation's expectancies and reassurance focused on him, as emphasized by Sillman.[8] It is through these means that he can achieve conviction and function efficiently in the face of the overwhelming destructiveness of modern war.

Associated with the utilization of projection and introjection in securing loyalty is the use of group activities. The individual's activity and personal participation in group work and group meetings is of great value in receiving the effects of introjection. Large mass meetings are useful for intensifying loyalty.

A third method for intensifying loyalty is by pointing out clearly that democracy is a unique and fragile achievement. One of the well established methods for safeguarding the feeling of love for an object is the threat of loss. Too many people assume without evidence that there is a biological drive within man for freedom and democracy. Deeper studies of the mind reveal that man's fundamental nature tends to be inimical to democracy. The individual and the nation are faced with the extermination of the most precious social achievement of all history.

A fourth method of intensifying the individual's feeling of loyalty is related to the second major phase of education to war, namely, the externalization of aggression. This is based on the deeper significance of loyalty which is fundamentally a derivative of the parental identification the individual develops in childhood. Due to the prevalence of unconscious hos-

tility against love objects, in order to intensify affection, it is necessary that the hostility also be discharged. For maximum effectiveness this must obviously be directed against the enemy. Everything should be done to make the soldier think of himself as the protecting father of his democracy.

Complete externalization of aggression is the surest way to avoid the tendency toward internalization which may produce suicide and war neuroses. Training is needed which will produce a feeling of aggression against the enemy to the point where the danger from the enemy is completely ignored.

The fact of being an American must be carefully glorified. All emphasis must be placed on the achievements of America. It is only through the awesome respect of the American ideal that the individual can be brought freely to make the sacrifice necessary for the survival of the nation.

Acknowledgment of the individual as an American, with the obligations and privileges the term implies, will effectively externalize his aggression. There is probably no soldier as efficient as he who fights for a passionate ideal compared to which his life is of small value.

Essentials for Adjustment

1. Crystallization of aims and ideals.
2. Intensification of loyalty.
3. Externalization of aggressiveness.
4. Condensation of sentiments.
5. Use of group activities.
6. Threat of loss of freedom.
7. List crimes of enemy:

    a. Rotterdam.
    b. Lidice.
    c. Mass reprisals.
    d. Treaties as scraps of paper.

8. Demonstrate lust for war as national policy of enemy.

In total war every citizen has a contribution to make. The inability of many to qualify for active military service frees them for utilization in non-combat pursuits, industrial plants, home defense, and innumerable other activities. To fulfill the obligations of citizenship requires that these individuals likewise maintain a vigorous state of health and high morale to attain the stability that is part of their contribution.

LIMITED SERVICE

Rejection from an active part in a military organization need not exclude the willing individual from making a useful contribution to the war effort. Indeed, the appointment of individuals with physical disabilities in civilian jobs, thereby freeing able bodied men for military service, constitutes a

resourceful utilization of manpower. Likewise, the women of the nation are rising magnificently to the national challenge by applying in large numbers for jobs heretofore regarded as requiring able bodied men. Women workers in industry, war plants, railroads, and numerous hazardous pursuits excite the admiration of the entire nation.

The Malingerer: A small group of the population fails completely to grasp the meaning of citizenship. They are willing to accept all of the privileges but eager to escape obligations, particularly in time of war. The malingerer in industry is well known, and the psychiatrists on induction boards are quick to spot the weakling who does not want to carry his share of the national burden. Curiously, malingerers rarely try to simulate mental disease as a means of avoiding military service. In order to be fair with this group a trial period may be advised for the purpose of straightening out minor reaction kinks. On the other hand, military authorities can not have their time engaged in nursing misfits, nor should society unload social undesirables into military service.

THE TRAINING PERIOD

The impact of war on the civilian population precipitates a situation requiring a high degree of adaptability to a new way of life for the average American. The need for adjustment is evident. The most common basis for maladjustment is anxiety, clearly defined by Whitehead[9] as "mental uneasiness arising from fear or distress, eager desire, concern." A moderate degree of anxiety is experienced by the majority of normal individuals and may act as a driving force for effective adjustment.

Anxiety, however, may exist to such an extent as to incapacitate the individual for useful service. Anxiety may show itself as a psychosomatic constellation with functional disturbances of the major body systems; it may produce excitement with trembling, perspiration and similar effects of the autonomic nervous system; it may precipitate a vicious circle in the form of worry which vitiates the individual's ability for accomplishment.

Anxiety may likewise bring about the more vague manifestations of a neurosis such as mild depression, headache or other body aches and pains or pronounced fatigue.

Adjustment problems may arise:

1. When the individual finds himself facing an impending military career.
2. When he is separated from his family.
3. Soon after induction, especially in those lads who have never been away from home.
4. Early in the preliminary period of training.

Episodes in the experience of the embryo soldier are clearly understood by psychiatrists, but there is a pressing need for a wider knowledge on the part of the medical profession as a whole in order that adequate safeguards may be created at the appropriate time.

On entering the training period, the healthy recruit finds the new life with its variety of new experiences an interesting one and receives from his buddies stimulating support that is effective in maintaining morale. · The sensitive lad often finds adjustment a painful process. However, unless there is an underlying predisposition to a neurosis, this type of recruit, as a rule, will compensate for earlier lack of experience and ultimately becomes good officer material.

Modern war is a highly specialized activity. Recruits need be classified according to their adaptability for various specialized fighting services, such as engineers, infantry, submarines, tanks, etc. In the Canadian army, the doctor draws a profile, and the Army fits the man to the job. Each recruit is classified according to the physique, upper arms, legs, hearing, eyesight, and mental stability. This system, according to Meakins,[10] has worked out satisfactorily.

Military life is an active career, and associations and duties are definitely planned by superior officers for producing vigorous and healthy soldiers with a foreknowledge of the emotional turmoil that exists in many of the lads just coming into training.

The army has established nine rehabilitation camps to redirect men who have committed non-criminal minor offenses such as absence without leave and insubordination. These men spend half a day in hard work and military drill; the remainder of the day is devoted to an educational program including military and ethical lectures using the resources of psychology. When it is deemed advisable, these men are returned to an "honor company" where they are trained substantially as regulars.

IN ACTION

Fortunately, psychiatric military services today are so well established that frank misfits and borderline cases are for the most part screened out so that only the healthiest members from the recruited groups are subjected to active combat.

It is a curious fact, as related by many soldiers who have been in action, that minor wounds sustained in combat, far from being incapacitating, act as a stimulus to heighten individual action. On the other hand, when a fellow soldier reveals an emotional strain preceding, or in action, it has, at times, a disheartening effect on those near him if they have time for observation. Whitehead[9] points out that the principal stresses and strain under combat are minimized as the man becomes hardened to battle, as has been proved by the use of experienced troops who have been many times under fire. These stresses and strains have been classified as:

1. Noise and confusion of battle.
2. The constant threat of death.
3. Observing the destruction of fellow soldiers.
4. Exhaustion and hunger.

Exhaustion is difficult to avoid when troops must be kept on the alert and ready for action over long periods of time. The problem of hunger, which is important also in maintaining high morale is, of course, a responsibility of service and supply.

A high state of morale is essential for success in battle. The well adjusted soldier has a wholesome respect for himself as well as for his fellow man. The neurotic soldier, overburdened with an anxious sensation, may be the instrument for his own and his mates' destruction. As morale falls, neurotic tendencies come to the surface.

THE HOME FRONT

As previously noted, every individual destined for action may experience periods of anxiety, a normal component of every soldier. Coupled with the morale of the fighting unit, and of equal importance, must be the knowledge by the troops that the home front is militantly supporting his every act. Cheerful news from home and knowledge that production is at the high point, that the home community is coming through with the equipment which the fighting soldier needs, are absolutely essential in war time.

In global war, civilian morale is of equal importance to that of the military. In total war, the civilian is a part time soldier and his pursuits are divided between civilian and military duties. Strecker[11] points out that functional symptoms are comparatively rare among civilians, but that when they do occur they are essentially of the same type based on anxiety. Curiously, it is the civilians who habitually seek shelter in the deeper bombproofs, who are most affected by the fear of raids, whereas those civilians with duties connected directly with the bombing, who are active in first-aid groups, or with the fire fighters and others, will show a remarkably low percentage of neuroses. It is generally accepted that the greater the sense of individual responsibility, the less is the likelihood for an inadequate reaction, that is, the better adjusted is the individual.

Strecker[11] makes a point of two emotions which stand out prominently in the British make-up, namely, infinite patience and pity that only slowly turns to anger. The British sense of detachment is important in maintaining both civilian and military morale, but finally the key to the quiet endurance of the average Briton is the knowledge that he is a free man and today he has a positive aim.

The relatively remote geographical position of our nation, which renders it less liable to bombing such as the British Isles have experienced, has kept from the American people the emotional drive for action which appears immediately after an air attack.

A high state of civilian morale requires certain fundamental health requisites be maintained. In the presence of food rationing and round-the-clock industrial activity, the population at large needs to realize that in peace

time the individual's average daily food intake is probably twice as much as his body requires, and that rationing does not of necessity reduce physical efficiency. It is largely a state of mind.

It is of importance for industry to understand the need for adequate rest and hours of recreation for industrial workers who are driving hard while at work for utmost production. The human body is not so constituted as to be able to maintain an efficient production long hours each day seven days a week without precipitating a breakdown.

Fatigue is one of the most important problems today in civilian existence and industry, as in military life, since it has a direct bearing on the morale of everyone. Therefore, working hours and military activity need be planned, insofar as possible, to maintain optimum efficiency and minimize the precipitation of neurosis.

The Britons have demonstrated that communities may become accustomed to repeated bombings and even though large numbers of the population may appear severely ill and are brought into hospitals in a state of shock, they seem to make a prompt recovery and are fit for discharge in a very few days.

The Future's Promise

A satisfactory adjustment in time of war is facilitated by a clear understanding of the ideals the nation is fighting to maintain. War has been described as a means of resolving an intolerable situation. Lack of appreciation of this fact on the part of the public and the military may bring disaster, since it goes hand-in-hand with aversion to an all-out effort for victory.

The world is moving in new directions, and nostalgia for the good old days must give way to a driving desire for a realignment of social forces in the interest of society as a whole. Democracy, if it is to be preserved, will require a more intimate participation on the part of citizens today and tomorrow in its protection. Universal military service in the broadest sense and on the part of all able-bodied students of college and secondary school rank needs to become a national instrument and should not be regarded as compulsory, but rather as a privilege and obligation.

To shorten the present conflict with the saving of many lives, otherwise needlessly lost, there needs be a militant campaign through press, radio, pulpit and public forum to emphasize more forcefully the ideals for which we, as a nation, are fighting. Schools throughout the land may contribute immeasurably to the war effort by teaching students the real meaning of freedom, inculcating in the new life blood of the nation a burning desire to participate in the largest possible way in the movement that constitutes the war effort.

Adjustment to war on a national scale is the result of personal acceptance by every citizen of his primary obligation to his native land. The concept of the brotherhood of man with equality of opportunity for all must replace the doctrine of the master race as an instrument of nations. We are all voyagers

aboard this planet on the sea of life, and if too many rock the boat, civilization itself may be lost.

BIBLIOGRAPHY

1. REES, J. R.: Three years of military psychiatry in the United Kingdom, Correspondence de Napoleon, 18, 14276: 1808, Brit. Med. Jr., Jan. 1943, No. 4278, pgs. 1–6.
2. ROWNTREE, LEONARD G.: Colonel, Chief of Medical Division of National Selective Service, April 2, 1943 (The New York Times)—speaking before the War Physical Fitness Training Institute at Teachers College, Columbia University.
3. THOM, D. A.: War neuroses, New England Jr. Med., 1941, ccxxv, 864–867.
4. GILLESPIE, R. D.: Psychological effects of war on citizen and soldier, Brit. Med. Jr., Jan. 30, 1943, No. 4282, pg. 133.
5. STRECKER, EDWARD A.: Personal Communications.
6. FAIRBAIRN, W. RONALD D.: The war neuroses: their nature and significance, Brit. Med. Jr., Feb. 13, 1943, No. 4284, 183–186.
7. PEGGE, G.: Correspondence, Brit. Med. Jr., March 13, 1943, No. 4288, pg. 333.
8. SILLMAN, L. R.: Psychiatry and morale, Jr. Nerv. and Ment. Dis., xcvii, 283–295.
9. WHITEHEAD, D.: The psychoneurosis in military medicine, Pennsylvania Med. Jr., 1942–43, xlvi, 463–468.
10. MEAKINS, JONATHAN C.: Personal Communication.
11. STRECKER, E. A.: Fundamentals of psychiatry, 1942, J. B. Lippincott Co., Philadelphia.

NEUROGENIC POLYCYTHEMIA [*]

By Gurth Carpenter, M.B., M.R.C.P., *Los Angeles,* Henry Schwartz,
M.D., *St. Louis,* and A. Earl Walker, M.D., F.A.C.S.,
Chicago, Illinois

Introduction

The cause of so-called polycythemia rubra vera is at present not known. It seems possible that it is a symptom complex which future observation will classify into a number of different types.

The signs and symptoms of neurological involvement in polycythemia rubra vera occur with extreme frequency (Osler,[25] Christian,[8] Mendel,[22] Brockbank[4]), and indeed "it appears that neurologic manifestations are among the commonest symptoms in polycythemia vera" (Sloan[30]).

However, the association of polycythemia rubra vera with intracranial neoplasia is an event of the greatest rarity, and there is no detailed report in the literature of its occurring with a subtentorial tumor. The observation, therefore, of a case in the University of Chicago Clinics (G. C. and E. W.) and separately a case in St. Louis (H. S.), of instances of well marked polycythemia in which the red blood cell count returned to normal following the surgical extirpation of subtentorial tumors is worthy of publication. It is surprising that in each instance the neoplasm was a hemangioblastoma, a rare intracranial growth, though it is not clear what interpretation should be placed on this occurrence.

Case Reports

Case 1. M. A., a 52 year old laborer, was referred to the University of Chicago Clinics by Dr. E. Walshe, September 19, 1940, with the complaints of weakness, headaches, constipation of one year's duration, and vomiting of three months' duration. The history was unsatisfactory because of the patient's slow mentation and confusion. The family did not prove helpful witnesses.

He was well until one year previously, when he commenced to have vertical headaches and constipation. He became increasingly weak, finally unable to stand, and six months prior to admission he took to bed. A coarse intention tremor of all the extremities developed. When attempting to walk with assistance, his legs would become stiff. In the three months prior to admission he had had three attacks of sudden projectile vomiting. His son and daughter had noted his mental slowness, but no loss of orientation or memory. He did not complain of visual disturbances. .

The patient was a thin, tremulous individual with greatly retarded mentation. At times he displayed a coarse tremor of the hands. He weighed 132 pounds, and was 70 inches tall. External examination showed loose inelastic skin with marked facial rubor and congestion of the small veins of the skin and conjunctiva. The mouth was edentulous, its mucous membrane markedly reddened. The neck and thorax were .

normal. He complained of tenderness when pressure was exerted over the lower lumbar spine. The patient held his back rigid and refused to bend forward. No abnormalities were noted in the heart or lungs. No organ appeared to be enlarged within the abdomen; in particular the spleen was not enlarged to palpation or percussion. No clubbing of the fingers was present. His blood pressure varied between 158 mm. Hg systolic and 120 mm. diastolic and 170 mm. systolic and 120 mm. diastolic.

The hematological findings are given in the accompanying table (table 1).

TABLE I

Blood Findings (case 1)

Date	RBC (cu. mm.)	Hgb. gm.	WBC (cu. mm.)	Cell Vol. %	Differential, Hematocrit, etc.
9-19-40	6,830,000	23	6,600		P. 65%, lymph. 22%, monocytes 8%, eosinophiles 5%
9-24-40	7,130,000	22	6,200	68%	P. 79%, lymph. 18%, monocytes 3%, reticulocytes 0.3% MC vol. 95.3 MC Hgb. 29.3
9-26-40				68	Bl. volume 7,125 c.c. Vol./kilo 105.5 c.c. Red cell mass 4844 c.c. Vol./kilo 73.2 c.c.
9-28-40	500 c.c. blood removed				
10-1-40	6,820,000	18	7,600		
10-3-40	Operation and Transfusion of 500 c.c. whole blood				
10-4-40	6,720,000	18	9,300		
10-5-40	5,360,000	15	9,300		
10-7-40	4,840,000	14.2		46	MC Vol. 97.1 MC Hgb. 29.3
10-16-40	4,660,000	13.6		44	
12-18-40	4,660,000			41	Blood volume 5356 c.c. Vol./kilo 73.7 c.c. Red cell mass 2195 c.c. Vol./kilo 29.8 c.c.
11-7-41	4,040,000	14.0	5,200	42	Reticulocytes 0%, P. 53%, large lymph. 2%, small lymph. 32%, monocytes 11%, eosinophiles 2% Bl. volume 5124 c.c. Vol./kilo 68.3 c.c. Red cell mass 2152 c.c. Vol./kilo 28.8 c.c.

The patient was seen by the neurological service in consultation six days after admission. At that time he was disoriented. There was a bilateral papilledema of three diopters. The visual fields were full. External ocular movements were full and steady. The pupils were 3 mm. in diameter and reacted well to direct light. There was no other evidence of cranial nerve dysfunction. The tendon reflexes were active and equal, and both plantar reflexes were flexor. Sensation appeared normal. The neurologist was impressed by the great effort exerted by the patient in carrying out simple movements and bizarre tremors of the extremities on voluntary movement. It was considered that his neurological difficulties were "associated with his systemic disease," but that "he had also a great many signs of conversion hysteria."

Urinalysis showed no abnormality except for one to three white cells per high power field. The Wassermann and Kahn reactions of the blood were negative. The serum calcium was 10.4 mg. per cent, and the serum potassium 3.7 mg. per cent. The phosphatase activity of the serum was 2.6 units (normal). The total plasma proteins were 6.3 grams per cent. An electrocardiogram showed a sinus tachycardia but no other abnormalities.

A roentgenogram of the chest revealed normal lung parenchyma, but there was spectacular calcification of the mesenteric lymph nodes and osteoarthritis of the spine. Roentgenograms of the skull showed a small area of calcification within the brain substance of the right parietal lobe.

A lumbar puncture was performed. The initial pressure was 320 mm. of spinal fluid. The Pandy reaction was negative, and there were six cells per cu. mm. of spinal fluid. The total protein was 32.5 mg. per cent. The Lange curve was 0011100000.

Because of the intracranial pressure the neurosurgical service was asked to see the patient regarding the advisability of subtemporal decompression. At that time, September 30, 1940, the patient was disoriented as to time, place and person. He was unable to carry out simple mentation. His neurological findings were much the same as at the earlier examination.

Because of the history, the severe nervous manifestations, and relatively few peripheral signs of polycythemia it was suggested that ventriculography be used in order to eliminate the possibility of an intracranial neoplasm in association with the systemic disease.

On October 3, 1940, under local anesthesia, bilateral perforations were made in the occipital regions. The right ventricle was reached at a depth of 5 cm. and the left with some difficulty at 5.5 cm. Clear, colorless fluid gushed out under obviously increased pressure. Approximately 120 c.c. of ventricular fluid were removed, and 100 c.c. of air injected into the ventricular system.

Roentgenograms taken following this procedure revealed a marked symmetrical dilatation of the ventricular system including the third and fourth ventricles with a small filling defect in the latter ventricle.

The patient was immediately returned to the operating room and anesthetized with ether. The posterior fossa was explored through a curved horizontal incision in the occipital region and subperiosteal dissection of the suboccipital muscles. The bone was perforated and the opening enlarged to the foramen magnum. The dura mater was incised transversely, but in carrying the incision on the right side considerable bleeding was encountered from vessels of the cerebellum adherent to the dura mater. The dura mater was finally elevated disclosing a number of large vessels over the surface of the right cerebellar hemisphere. Upon attempting to puncture the right cerebellar hemisphere, marked resistance and profuse bleeding were encountered. The cerebellar cortex was incised and at a depth of 1 to 2 mm. a reddish encapsulated tumor covered by numerous venous channels was found. The cerebellar tissue was dissected from about the tumor, and the vessels clipped and cut as encountered. As the vessels were clipped and the blood supply cut off the tumor noticeably shrank. The tumor was attached superiorly to the torcula Herophili and extended about 4 cm. to the right. When the tumor had been dissected free on all sides except from its connection to the torcula, it was lifted from its bed, the pedicle tied and cut. Several bleeding points along the torcula were controlled by muscle stamps. After complete hemostasis the dura mater was closed. The muscles were sutured to the superior nuchal line with deknatel and the skin margins approximated with two layers of black silk.

The patient had a relatively smooth convalescence. His confusion and disorientation slowly decreased but had not entirely disappeared at the time of his discharge two weeks after operation. He was able to walk, although unsteadily and on

a wide base. His visual fields were full but the visual acuity was diminished (R. E. 6/2000; L. E. 10/20). The optic discs were still elevated 2½ diopters.

The patient returned to the out-patient department on October 30, 1940. He had no complaints. He was well oriented in all phases. His gait was still on a wide base but he walked steadily.

He has been seen on three subsequent occasions. At the time of his latest visit to the Clinics, November 7, 1941, he had no complaints except for a slight dizziness on upward gaze, which he had experienced for approximately one week. He had been working as a laborer.

FIG. 1. Photomicrographs of sections of the tumor (case 1) stained for cells (hematoxylin and eosin) at the right and for reticulin (Perdrau) at the left (× 115).

Neurological examination at that time was normal except for the findings refer-able to the eyes. He could see form poorly with the right eye but with the left eye was able to read news print. Both discs were pale, flat and the margins indistinct.

Tumor. The tumor measured 3.5 by 3.5 by 2.5 cm. It was reddish brown and firm except for a cystic area about 2 cm. in diameter. Over its surface were numer-ous small and large blood vessels, some of which were clipped.

Microscopic examination of the tumor revealed it to be composed of closely packed capillary-like spaces lined by a single layer of endothelial cells. Between these spaces were masses of cells having round nuclei and a moderate amount of chromatin with nonstaining cytoplasm, closely resembling endothelial cells. Perdrau sections revealed an intimate network of reticulin and collagen surrounding the capil-lary spaces and about the cells. The tumor was a hemangioblastoma (figure 1).

Comment. From a diagnostic standpoint this case presented an interesting problem. Certainly all the findings present at the time of the clinical examination might have been the result of the polycythemia. However, the history of marked unsteadiness of gait shortly after the onset of symptoms suggested a cerebellar lesion. The marked papilledema and intracranial hypertension seemed out of proportion to what might have been expected if the intracranial disease were entirely on the basis of polycythemia.

Although hemangioblastomata of the cerebellum are frequently associated with retinal vascular malformations or angiomata, no such ocular lesion could be found on repeated examinations in the present case.

Case 2. W. Z., a 29 year old white printer, was admitted to the Deaconess Hospital, St. Louis, on March 16, 1941, on the neurological service of Dr. A. H. Deppe. He complained of headache. There was no history of weakness, vomiting, staggering gait or incoördination. Two years previously he consulted an ophthalmologist who prescribed glasses. These were worn chiefly at work. One week before admission, he again consulted his ophthalmologist, who observed papilledema of both discs and referred the patient to Dr. Deppe. Two years before the present illness, the patient had had a lymph gland removed from the region of the right nipple; according to the patient this was not malignant. Six months before admission a "cyst" was removed from the back of his neck. No details concerning this lesion could be obtained. The patient's wife had multiple sclerosis.

On admission, bilateral choked discs were noted. Neurological examination was otherwise negative, except for a questionable sensory disturbance at about the fourth cervical dermatome. A spinal puncture revealed an initial pressure of 330 mm. of

TABLE II

Blood Findings (case 2)

Date	RBC (cu. mm.)	Hgb. (gm.)	WBC (cu. mm.)	Differential, Hematocrit, etc.
3-17-41	5,960,000	18.4	9,150	Seg. 46.5%, Band 17.5%, Lymph. 32.5%, Mono. 1%, Eos. 2.5% Clotting time 3′ 15″
3-26-41	6,500,000	20	8,300	Seg. 38.5%, Band 12.5%, Lymph. 42%, Mono. 1%, Eos. 6% Platelets 295,000
3-28-41	Operation with Removal of Tumor			
4-12-41	4,390,000	13	10,950	Seg. 55.5%, Band 14%, Lymph. 30.5%, Platelets 184,900
7-17-41	6,250,000*	14.7	10,150	
7-30-41	5,100,000	17.2	6,000	P. 56%, Lymph. 25%, Mono. 7%, Eos. 10%, Reticulocytes 4%. Platelets 918,000 MC Vol. 85 MC Hgb. 31 MC Conc. 37
11-5-41	4,780,000	14.0		

* This blood count was performed by a different technician than the others in the series. The recorded red cell count is out of keeping with the recorded hemoglobin level.

spinal fluid. The Wassermann test on this fluid was negative. Roentgenograms of the skull and cervical spine showed no abnormality. The hematological findings are given in the accompanying table (table 2).

A neurological consultant on March 25, 1941 (H. G. S.) found the patient to be clear mentally, rational and coöperative. He was well-developed and well-nourished. His blood pressure was 110 mm. Hg systolic and 80 mm. diastolic. There was marked choking of both discs with complete obliteration of the disc margins, and numerous hemorrhages. The visual fields were full. The pupils were equal and reacted well, eye movements were well performed, without nystagmus. The other cranial nerves were intact. Power in all extremities was good. Fine movements were well performed. There was no ataxia or adiadochokinesis. The patient stood well in the Romberg position. The gait was normal. The tendon reflexes were active and equal on both sides. There were no pathological toe signs or clonus. No sensory disturbance could be made out.

The possibility that the polycythemia was the sole cause was considered, but the absence of other central and peripheral nervous system signs made this doubtful. Ventricular air studies were advised, to be followed by surgical extirpation of a tumor, if indicated; or, if ventriculograms were negative, it was planned to perform a subtemporal decompression to save the patient's vision.

On March 28, 1941, under avertin-local anesthesia, bilateral perforator openings were made in the parieto-occipital region. The occipital horn of the right ventricle was punctured, and about 100 c.c. of fluid were replaced with 90 c.c. of air. Films showed symmetrical dilatation of both lateral ventricles and the third ventricle.

The patient was taken back to the operating room for suboccipital craniotomy. A mastoid-to-mastoid skin incision was made. The occipital muscles were cut and stripped away from the occipital bone. The bone was then removed laterally as far as the mastoid emissary veins, and superiorly as far as the transverse sinus. After ventricular puncture to reduce pressure, the dura was opened over both cerebellar hemispheres. The occipital sinus was ligated with a transfixed suture, and cut across. The cisterna magna was completely obliterated by the cerebellar tonsils which were herniated far down into the cervical canal. The hemisphere on the left was swollen. The lamellae were flattened out, and laterally had a distinctly yellowish color. At the left lateral angle of the field several large vessels were found running from the hemisphere to the dura mater. These vessels were coagulated and cut. After coagulation of the superficial vessels, the hemisphere was incised, and the surface of a rather firm, extremely vascular tumor immediately came into view. The tumor was enucleated by blunt dissection. One large vessel running from the tumor to the petrosal sinus was coagulated and cut. The tumor was then lifted out. It had not involved the cerebellar nuclei. After removal of the tumor, in order to free the cerebellar tonsils, it was necessary to rongeur away the arch of the atlas and split the dura down to the second cervical vertebra. After complete hemostasis, the wound was closed in layers with silk sutures.

The postoperative course was uncomplicated, and the patient was discharged from the hospital on April 13, 1941, sixteen days after operation. At the time of discharge, the choked discs showed marked recession, the left fundus was normal, but the right disc margins were still blurred. Neurological examination was entirely negative. In particular, there were no signs referable to the cerebellum. On April 28, 1941, check-up examination showed very slight blurring of the right disc. One month later this had disappeared. The patient returned to work six weeks after operation. He has remained symptom-free and repeated examinations have revealed no neurological abnormalities.

Tumor. The tumor was oval in shape. It measured 3 cm. in its long axis, and 2.5 cm. in the short diameter. It was reddish-blue in color, and was of moderately firm consistency. Two large and many small blood vessels could be seen on the sur-

face. On cut surface, the color was more deeply red-brown, evidently due to blood. Microscopically, sections demonstrated tumor consisting of masses of endothelial-lined spaces within which were blood cells. There was an intimate network of reticulin. A diagnosis of hemangioblastoma was made (figure 2).

FIG. 2. Photomicrographs of sections of the tumor (case 2) stained for cells (hematoxylin and eosin) at the right and for reticulin (Perdrau) at the left (× 155). The delicate reticulin network about the cells and vessels is particularly well shown.

Comment. In this as in the first case the diagnosis was difficult and only after ventriculography could it be said with certainty that the patient had an intracranial tumor.

That the second patient had no clinical findings pointing to the cerebellum is probably due to the location of the tumor in the lateral part of the left cerebellar hemisphere without involving the cerebellar nuclei. Even large tumors in that region fail to produce cerebellar signs. Tumors situated near the midline interfering with the function of the vermis cerebelli give rise to disturbances of equilibrium such as those that initiated the first patient's illness.

It is remarked that in neither of these patients was there any evidence of dehydration which might in itself give rise to high erythrocyte counts.

In both cases the blood was examined on two or more occasions over a period of several weeks.

DISCUSSION

It is generally conceded that intracranial lesions are frequent occurrences in polycythemia rubra vera. The common attitude toward this relationship was stated emphatically by Brockbank [4] in remarking that the nervous lesions may be regarded invariably as a function of the primary polycythemia.

However, the past two decades have seen the contribution of a small volume of literature which is devoted to the thesis that polycythemia may be due to lesions in the brain substance. It is stated (Ferraro and Sherwood [12]) that the increased incidence of encephalitis lethargica during this period, with its destruction of the vegetative centers, is directly responsible for the increased incidence of these observations.

For the most part, unfortunately, the reports of neurologic damage causally related to polycythemia do not bear critical analysis. First, the evidence of neurologic damage is based largely on clinical examinations and only in one or two cases controlled by anatomic or pathologic observations. Secondly, the blood counts submitted are often border-line and not conclusive of polycythemia, and rarely accompanied by further evidence such as blood volume studies, reticulocyte counts, and other pertinent data. Thirdly, the situation is further confused by the proximity of the pituitary gland to the vegetative centers; the occurrence of polycythemia in the course of various pituitary-adrenal syndromes (particularly the Achard-Thiers-Cushing syndrome) has been accorded general recognition during the past 10 years.

Moreover, a great number of the reports of polycythemia allegedly due to intracranial lesions come from countries bordering upon the Mediterranean basin. During the last five years it has become increasingly evident (Caminopetros,[5] Wintrobe et al.[33]) that moderate polycythemia, often with low hemoglobin values and active reticulocytosis, occurs in familial distribution in the Mediterranean races representing some forme frustre of the Cooley syndrome (Mediterranean anemia). It is to be noted, for instance, that a number of the cases presented by DaRin and Costa [9] as instances of polycythemia associated with neurologic lesions had very low hemoglobin values and reticulocytosis up to 5 per cent.

Because of these circumstances it is not proposed to give here an analytical discussion of all the reported cases in which polycythemia was the alleged result of intracranial lesions. Adequate reviews of these cases can be found in the papers of DaRin and Costa,[9] and of Ferraro and Sherwood.[12] Excluding those cases with intracranial neoplasm the greater proportion of this group suffered encephalitis, or some episode interpretable as such (Schulhof and Mathies,[29] Ceccini, Ronchetti and Gasparin,[7] Salus,[27] Riccitelli,[26] DaRin and Costa,[9] Munzer,[23] Hoff,[17] Gunther,[14] Ferraro and Sherwood,[12] and others), whereas others displayed miscellaneous causes for intracranial damage such as concussion (Hecht and Weil,[16] Guillain, Lechelle

and Garcin,[15]), Huntington's chorea (DaRin and Costa[9]), embolism (Da-Rin and Costa[9]), alleged central nervous system syphilis (Lhermitte and Kyriaco[19]), paralysis agitans (Ferraro and Sherwood[12]), and carbon monoxide poisoning (Dittmars[11]). From the frequency with which obesity, polyuria, and narcolepsy were seen in association with the other neurological manifestations (Kraus,[18] Munzer,[23] Gunther,[14] Salus,[27] DaRin and Costa,[9] Thiele and Bernhardt[31]) it was generally concluded that the essential lesion was in the diencephalon. But in no case in this group was anatomic evidence produced.

A small body of experimental work has been adduced to support the possible presence of a center for regulation of the erythrocyte level in the diencephalon. In 1927 Schulhof and Mathies[29] injected sclerotic agents approximately in the region of the "proximal vegetative centers" in three rabbits, in all of which there were increases in erythrocyte level of at least twice the mean deviation of counts in their normal rabbits. This report was apparently meant as preliminary, but was unfortunately never followed up with longer series, nor with anatomic studies. DaRin and Costa,[9] and Riccitelli[26] also claimed to have caused polycythemia in rabbits by damaging the diencephalic region. According to Ginsberg and Heilmeyer[13] various disturbances of the central nervous system of human beings (encephalography, lumbar puncture, concussion, epileptiform seizures) may produce reticulocytosis up to 4 per cent.

Opposite to this discussion is mention of the well controlled work of Schafer[28] in producing erythremia up to 9 million red blood cells per cu. mm. in dogs by section of all afferent depressor fibers in the cervical region. The great increase in blood volumes accompanying the polycythemia was shown to be due entirely to increase in the cell volume. Total sympathectomy abolished or prevented this effect. Hypertension with vasoconstriction is an essential part of the syndrome produced by depressor section, and it is possible that the operation presents nothing else than a surgical method of producing the type of polycythemia which Davis[10] has produced in man and animals with vasconstrictor drugs. On the other hand, its implications insofar as possible erythrocyte controlling centers are concerned cannot now be discounted. In this relation we should note that the considerable hypertension present previous to operation in case 1 (158 mm. systolic and 120 mm. diastolic; 170 mm. systolic and 120 mm. diastolic) disappeared after operation. This naturally brings to mind the possible association of this case with the type of polycythemic hypertension observed in Schafer's dogs. In case 2 no increased blood pressures were recorded.

The diagnosis of intracranial neoplasms in the presence of polycythemia may be difficult. Vascular lesions may well lead to false localizing signs, choked discs may be found (Lucas,[20] Parkes Weber[32]), and the cerebrospinal fluid pressure may reach 500 mm. of cerebrospinal fluid (Bottinger[3]). Thus, a number of cases have been explored for tumor, and none found (Christian,[8] Oppenheimer,[24] Brockbank[4]).

Relatively few reports of the association of polycythemia with intracranial neoplasms are found in the literature. A number of these neoplasms were associated with the pituitary-infundibulum, and their endocrine status cannot be established. Thus, Castex[6] reported a tumor of the hypophyseal region with a red blood count of 7,500,000 per cu. mm. DaRin and Costa[9] saw two patients with a stated diagnosis of tumor of the base of the third ventricle with counts of 5,800,000 per cu. mm. and 6,790,000 per cu. mm. respectively (in both these cases the color index was given as approximately 0.5 and the reticulocyte levels 5 per cent and 4 per cent. This raises the question of the familial hypochromia of Mediterranean peoples mentioned above). Guillain, Lechelle, and Garcin[15] reported two instances of the adipose-genital syndrome, one with diabetes mellitus, a red cell count of 6,200,000 and a "meningioma or sarcoma" of the base of the brain; the other with infantilism, a red cell count of 6,380,000 per cu. mm., with a "tumor of the pouch of Rathke." These authors reported a further case with acromegalic symptoms, enlarged sella turcica, and red cell count of 6,510,000 in which following the removal of an "adenoma of the hypophysis" the count declined to figures of 4,760,000 and 4,805,000 per cu. mm. a year after operation. (This must be regarded as probably an endocrine tumor.) Baserga[2] contributed the case of a patient with a red cell count of 6,101,000 per cu. mm., with adiposity and restriction of the temporal visual fields, in which the given diagnosis was "tumor of the hypophyseal stalk." This patient had a total blood volume of 6522 c.c.

Three cases have been described with tumors other than of the diencephalo-pituitary region. Salus's[27] patient suffered paralysis of the right arm and leg, with Jacksonian attacks, and had red blood cell counts of 6,900,000 and 6,480,000 per cu. mm. There were polyuria, glycosuria, and impotence as possible evidence of diencephalic disturbances. *At autopsy* was found a "sarcoma of the left cerebral hemisphere."

Oppenheimer[24] stated that he had "observed a case with diagnosis of polycythemia which *at autopsy* showed a cerebellar medulloblastoma." No details were given. This is the only instance in which polycythemia was said to have been associated with any type of lesion beneath the tentorium. Meiner's[21] patient had 8,500,000 red cells per cu. mm. and 138 per cent hemoglobin previous to operation on a right central degenerated glioblastoma multiforme (one of the rare instances in which a histologic diagnosis is given). Subsequent to operation normal counts were recorded, but the patient had a certain amount of diffuse roentgen-ray therapy.

In no instance of "neurogenic polycythemia" has there been described any notable enlargement of the spleen. Neither spleen nor liver was enlarged in either of our cases. This perhaps is in keeping with the conception of the erythremia as essentially symptomatic, it being widely held (though unproved) that splenic enlargement is due to the storage of cells unwanted by the circulation. From the hematologic point of view the absence of

leukocytosis and of reticulocytosis (case 1) is also in keeping with a symptomatic polycythemia.

That the pathological type of the tumor may have played an etiological rôle in the polycythemia does not seem probable in view of the fact that in a series of 14 other cerebellar hemangioblastomata none has had any evidence of erythrocythemia. Nor do Cushing and Bailey [1] mention such a complicating condition in their review of the subject.

Although it is well known that hydrocephalus due to fourth ventricle tumors does cause a dysfunction of the hypothalamic centers, it is difficult to understand the mechanism by which such a neoplasm could selectively influence one diencephalic function. And even were that possible, why should the tumors in our two cases have produced such selective alterations, and other tumors similarly situated and with equally severe hydrocephalus have failed to do so? These considerations make it difficult for us to assert a diencephalic origin of the polycythemia, although otherwise that appears to be the most likely explanation in the light of our present knowledge.

SUMMARY

1. Two cases are reported of polycythemia which disappeared on removal of cerebellar hemangioblastomata.
2. The mechanism of this erythremia is discussed. We believe it to be of neurogenic origin.

BIBLIOGRAPHY

1. BAILEY, P., and CUSHING, H.: Tumors arising from the blood vessels of the brain, angiomatous malformations and haemangioblastomas, 1928, Balliere, Tindall and Cox, London.
2. BASERGA, P.: Polyglobulie da lesioni diencephalo-ipofisarie, Policlinico (sez. med.), 1934, xli, 17.
3. BOTTINGER, A.: Über erhöhten Cerebrospinaldruck bei Polycythemie, seine Entstehung, seine klinische und therapeutische Bedeutung, Deutsch. med. Wchnschr., 1918, xliv, 669.
4. BROCKBANK, T. W.: Neurologic aspects of polycythemia vera, Am. Jr. Med. Sci., 1929, clxxviii, 209.
5. CAMINOPETROS, J.: Recherches sur l'anémie érythroblastique infantile des peuples de la Méditerranée orientale: étude nosologique, Ann. de méd., 1938, xliii, 27. Recherches sur l'anémie érythroblastique infantile des peuples de la Méditerranée orientale: étude anthropologique, étiologique et pathogénique; la transmission héréditaire de la maladie, ibid., 1938, xliii, 104.
6. CASTEX, M. R.: Eritrocitosis y eritremias etio-fisio-patogenias, Prensa med. argent., 1929, xvi, 693.
7. CECCINI, RONCHETTI, and GASPARIN. Cited by DARIN and COSTA.[9]
8. CHRISTIAN, H. A.: Nervous symptoms of polycythemia vera, Am. Jr. Med. Sci., 1917, cliv, 547.
9. DARIN, O., and COSTA L.: Influenza del sistema nervosa vegetativo centrale sul quadro ematio, Clin. med. ital., 1934, lxv, 303.
10. DAVIS, J. E.: The production of experimental polycythemia in dogs, rabbits and man by the daily administration of ephedrine and by amphetamine in dogs, Am. Jr. Physiol., 1941, cxxxiv, 219.

11. DITTMARS, P.: Zwischenhirnschädigung und Polyzythämie nach Kohlenoxydintoxikation, Deutsch. med. Wchnschr., 1939, lxv, 500.

12. FERRARO, A., and SHERWOOD, W. D.: Polycythemia in the course of neuro-psychiatric condition, Psychiatric Quart., 1937, xi, 19.

13. GINZBERG, R., and HEILMEYER, L.: Reticulocytosen und die zentralnervöse Regulation des Blutes, Klin. Wchnschr., 1932, xi, 1991.

14. GUNTHER, F.: Über "zerebrale" Polyglobulie, Deutsch. Arch. f. klin. Med., 1929, clxv, 41.

15. GUILLAIN, G., LECHELLE, P., and GARCIN, R.: La polyglobulie, avec ou sans érythrose, de certains syndromes hypophyso-tubériens, Ann. de méd., 1932, xxxii, 100.

16. HECHT, P., and WEIL, P.: Polycythemie und Hirnerschütterung, Aerztl. Sachsverstand. Ztschr., 1929, xxxv, 35.

17. HOFF, F.: Klinische Beiträge zur Frage der zentralnervösen Regulation des Blutes, Klin. Wchnschr., 1932, ii, 1751.

18. KRAUS, W.: Pilous cerebral adiposity: a new syndrome, Am. Jr. Med. Sci., 1915, cxlix, 737.

19. LHERMITTE, J., and KYRIACO, N.: Syphilis infundibulo-tubérienne (narcolepsie, diabéte insipide, obesité, amenorrhée), Rev. neurol., 1931, xxxviii, 801.

20. LUCAS, W. S.: Erythremia or polycythemia with chronic cyanosis and splenomegaly, Arch. Int. Med., 1912, x, 597.

21. MEINER, E.: Hirngeschwulst und Polyglobulie, Schweiz. med. Wchnschr., 1936, xvii, 388.

22. MENDEL, K.: Nervöse und psychische Storungen bei Polycythämie, Zentralbl. f. d. ges. Neurol. u. Psychiat., 1925, xli, 513.

23. MUNZER, F. T.: Zur Frage der symptomatische Narkolepsie nach Encephalitis lethargica, Monatschr. f. Psychiat. u. Neurol., 1927, lxiii, 91.

24. OPPENHEIMER, B. S.: Vascular occlusion in polycythemia vera, Trans. Assoc. Am. Phys., 1929, xliv, 338.

25. OSLER, W. M.: Chronic cyanosis with polycythemia and enlarged spleen, a new clinical entity, Am. Jr. Med. Sci., 1903, cxxvi, 187.

26. RICCITELLI, L.: Recherches sur les centres encéphalique de régulation chimique, chimico-physique, et morphologique du sang, Jr. de physiol. et de path. gén., 1934, xxxii, 25.

27. SALUS, F.: Zur zentral-nervösen Regulation des roten Blutbildes, Deutsch. Arch. f. klin. Med., 1933, clxxv, 214.

28. SCHAFER, P.: Body fluid changes in neurogenic hypertension and total paravertebral sympathectomy, Proc. Soc. Exper. Biol. and Med., 1942, ii, 327.

29. SCHULHOF, K., and MATHIES, M.: Polyglobulia induced by cerebral lesions, Jr. Am. Med. Assoc., 1927, lxxxix, 2093.

30. SLOAN, L. H.: Polycythemia rubra vera: neurologic complications; reports of four cases, Arch. Neurol. and Psychiat., 1934, xxx, 154.

31. THIELE, R., and BERNHARDT, H.: Beiträge zur Kenntnis der Narkolepsie, 1933, Karger, Berlin.

32. WEBER, F. P.: Polycythemia, erythrocytosis and erythremia, 1921, Lewis, London.

33. WINTROBE, M., MATTEWS, E., POLLACK, R., and DOBYNS, B. M.: A familial hemopoietic disorder in Italian adolescents and adults, Jr. Am. Med. Assoc., 1940, cxiv, 1530.

THE RÔLE OF CENTRAL FACTORS IN THE PATHOGENESIS OF RHEUMATIC DISORDERS *

By Ralph Pemberton, M.S., M.D., F.A.C.P., and C. Wesler Scull, Ph.D., *Philadelphia, Pennsylvania*

In the course of development of almost any chapter of medicine there are periods when it becomes appropriate and even necessary to correlate the results of various lines of research and experience, with the aim of formulating an hypothesis as to the nature of the processes concerned, and of surveying the possibilities in new lines of approach. The field of arthritis and rheumatoid diseases is no exception to this generalization but has not often been the subject of such attempts. One reason for this is that the field as a whole has. long been dominated by the view that infection accounted for it, both etiologically and therapeutically, and that other considerations were therefore largely irrelevant.

As long ago as 1920, following studies upon arthritics in the Army, one of the present writers [1] pointed out that various disturbances of physiology played a significant rôle and deserved closer scrutiny, especially as regards therapy. "There is strong evidence that infectious foci are not the only agents capable of starting a chain of events that results in rheumatism and arthritis. That this chain should be referable to one agent alone necessitates an assumption difficult of defense. It is safer, and certainly more reasonable, to believe that a variety of factors, many types of infection, exposure to cold and wet, chronic intestinal conditions of which we have only imperfect knowledge, and possibly even less ponderable glandular disturbances, may induce the substratum." This general viewpoint was long regarded in many quarters as somewhat academic except in the minds of a few close students.

There has recently arisen, however, as the result of cumulative experience, wide appreciation that the doctrine of focal infection does not operate, either etiologically or therapeutically, with such constancy as to justify the exclusive rôle formerly ascribed to it. There is, indeed, at present some danger that a negative iconoclasticism, developed in reaction to exaggerated emphasis upon the rôle of focal infection, will work injustice to countless arthritics by neglect of such focal infections as may be present and influential.

Whatever rôle may finally be ascribed to infection in the arthritic syndrome, it is fortunate that a lessened emphasis upon it has now opened the door more widely to other contemplations of the problem and indeed re-

quires that many considerations previously waived aside be given more attention.

Any hypothesis regarding the pathogenesis of the syndrome must provide, at least, some account of the means whereby etiologic, precipitating and sustaining factors, acting either singly or synergistically, produce the full complex of physiologic deviations which characterize the disease. It is natural and appropriate that many considerations of etiologic factors have been particularly directed toward explanation of the articular features of the syndrome. The systemic nature of rheumatoid disorders, together with the generally symmetrical distribution of the major lesions, is fairly well recognized. For this reason, among others, infectious factors have been widely studied, chiefly in relation to the possible presence of infective agents or their products within articular tissues. It has been tacitly assumed that microörganisms or their toxins or both, if carried by the vascular or lymphatic routes from a focus, such as tonsils, teeth or prostate, would become equally distributed and would thus account for the important symmetrical nature of the disease so far as articular involvement is concerned.

The conspicuous failure of most efforts to isolate such suspected microorganisms [2,3,4] from the joints by cultural technics has led to the view that infection should be dismissed from consideration, at least practically if not academically.[5]

Similarly, guided by the principle of economy of hypothesis, traumatic factors have been studied and emphasized, primarily in respect to the influence of physical wear and tear on a single component of the articular structure, viz., cartilage.[6] It has been tacitly assumed that wear and tear on various comparable joints of the two sides of the body are essentially equivalent, except in special cases, and hence afford an adequate explanation of the frequency of symmetrical distribution of articular lesions, especially in hypertrophic arthritis. According to this view the appearance of an arthritis in mid-life is due to the summation of the total number of traumata suffered by articular tissues incidental to the passage of years. However, even limited clinical observation is sufficient to reveal incomplete correlation between the frequency and intensity of trauma and the development of articular lesions in susceptible and less susceptible persons. For example, Heberden's nodes, lesions typical of hypertrophic or osteoarthritis, frequently develop in the hands of physically inactive women, whereas such lesions are usually absent from the hands of active typists of the same chronologic age.

In addition to the foregoing considerations, which suggest the inadequacy of certain over-simplifications of the pathogenesis of arthritis, viz., that it is due to infection and trauma acting directly and alone, it is to be further observed that the actual locomotor and general disability is rarely if ever fully measurable in terms of solely articular lesions. In addition to the articular

dysfunction most arthritics present varied and unmistakable evidence of systemic deviations to be discussed later. Unfortunately no single index of systemic imbalance, when used alone, has yet been demonstrated to provide a fully satisfactory measure of the patient's general clinical condition.

The blood reflects a part of the systemic illness of the arthritic. Although there is some correlation of certain cytologic variations of the blood with the duration and type of disease,[7] these do not, when regarded separately, afford a fully satisfactory measure of the nature of the patient's illness. Anemia is frequently present and is sometimes severe, particularly in the acutely ill atrophic (rheumatoid) arthritic. This anemia is generally described as secondary, but this designation suggests that the anemia is of minor importance. However, it bears a fundamental relationship to the illness of the arthritic. This anemia is normocytic or microcytic, and the cells are hypochromic. It does not appear to be referable to an increased rate of destruction of erythrocytes inasmuch as the recticularization, icteric index and urinary excretion of urobilinogen are within normal limits. Race[8] has pointed out that the level of pigments in blood plasma is actually subnormal. The bone marrow, according to Farrar,[7] shows an increased number of normoblasts and prenormoblasts. The anemia in many arthritics responds poorly to medication with iron and liver. It may appear even more refractory than the articular disorder, remaining even after the discomfort in the joints subsides. The pathogenesis of this anemia is not fully clear. In view of the juxtaposition of certain of the pathologic processes of arthritis to the hematopoietic centers of the bone, the anemia may be regarded as a part of the syndrome. The foregoing facts suggest that an interference with the mechanism of erythropoiesis is predominant although impaired nutrition and gastrointestinal absorption may avowedly be contributory.

A "shift to the left" of the polymorphonuclear leukocytes is often observed among this class of patients. Deviations from the normal physical qualities and chemical composition of the cell-free blood fluids also occur with significant frequency. The rate of sedimentation of red blood cells in the blood plasma of many arthritics is increased, in association with an increased viscosity of the plasma. The protein fraction of blood is often abnormal. Agglutinins for hemolytic streptococci are present in high titer as well as precipitins for certain fractions of these organisms.[9] The fibrinogen of plasma and the globulin of serum are frequently elevated to high levels. The albumin fraction is sometimes considerably lowered, especially in atrophic cases of long duration and intense activity. Hypertrophics present comparable deviations but of lesser magnitude.[10, 11]

Observations on the fixed tissues from the point of view of physical and chemical constitution yield data which are equally or even more significant as compared with those presented by the circulating tissue. Muscular atrophy is evident to even a superficial examination of the rheumatoid

arthritic.   Skeletal atrophy, together with atrophy of all structures of the joint, is likewise evident on roentgenographic study.   Both of these features provided a basis for the designation of the term "atrophic" to the syndrome of proliferative arthritis, now designated as rheumatoid arthritis (American Committee for the Control of Rheumatism).

A low-grade peripheral edema is evident in many arthritics.   Particularly conspicuous in the course of recovery is the reappearance of the interstices and tendons on the dorsum of the hand as the edema lessens and disappears. With convalescence the skin assumes an altered physical appearance characterized by apparent redundancy and fine wrinkling.   During periods of clinical activity the skin over the hands, wrists, ankles, tibias and knees may be shiny as well as edematous.   This sequence of changes in physical appearance is undoubtedly related to a change in the relative amounts of water in the dermal tissues.[12, 13]   The nature of this peripheral edema and the several factors which modify it are not wholly evident.   As regards measures influential in reducing this edema, there is evidence that nutrition, the kind of alimentation, and rest in recumbency, as well as salt intake, purgation and sweating, may play an important rôle.   In addition to these factors, which may influence the ebb and flow of fluid and thereby induce exacerbations or remissions of symptoms, are the cyclic alterations in the effective levels of certain hormones.   Estrogens and androgens both play rôles in the regulation of water metabolism.   In addition, the adrenocortical hormones are known to be involved in the disposition of salt and water in the body.   The symptoms of premenstrual tension, headache, stiffness and pain experienced by arthritic women can probably be referred to these factors.

Functional tests conducted on patients with rheumatic disorders reveal additional evidences of a departure from that "steady state" of the body as a whole, which characterizes normality.   Under conditions of moderate variations in water intake, for example, there is often revealed among arthritics a decreased range of variability of renal function.   Similarly gastric,[14] hepatic,[15] and gall-bladder functional tests [16] reveal departures from normal.   The gastrointestinal tract as a whole is often hypotonic and its motility diminished under dietary conditions which in the normal subject afford normal function.[17]

The vascular beds of the skin are objectively modified in many of the patients who present arthritic disorders.   These changes are shown by direct microscopic inspection and by skin temperature observations.[18]   Few capillaries are visible and the blood flow in them is often slow and irregular.   The average skin temperature is lower among many arthritics than among normal individuals subjected to the same environmental temperature.   The adaptation of these patients to moderate variations in environmental temperature likewise shows a diminished and presumably less efficient range.[19]

These data suggest that the arthritic presents a multiplicity of factors which collectively underlie or constitute his illness.   To attempt to show

that the complete clinical pattern presented by each patient develops from the operation of a single stimulus common to all patients would be almost a "reductio ad absurdum." It would be equally unreasonable to attempt to explain separately each congeries of deviations encountered in the arthritic as arising independently, without connection between the component parts of the full picture.

Within these broad limits, however, it is permissible to consider certain central influences, some of them operative even before the disease actually begins as a clinical entity. Data indicate that both rheumatic fever and hypertrophic arthritis occur more frequently in persons whose families present a history of rheumatic disease than among those families free from these disorders.[20, 21] There is also strong evidence to indicate that inherited susceptibility to rheumatic diseases is much greater among uniovular than among binovular twins.[22] These data tend to confirm the old concept of a rheumatic "diathesis," an inborn tendency toward the development of rheumatism. This may be more specifically described in terms of the factors constituting the "diathesis." It is assumed that the tissues of the rheumatic are more than normally susceptible to the influences of agents producing the disease. The manner in which this susceptibility develops may be classified under two main headings, viz., (1) as a consequence of body build, and (2) as a consequence of defects in local tissues. In respect to the first factor, it is generally believed that atrophic arthritis is more likely to appear in a person of asthenic type whereas hypertrophic arthritis occurs more frequently in the sthenic type. General body pattern is recognized as hereditary. In turn, it is also to be noted that differences in body build reflect differences in developmental influences. Of the recognized endogenous factors which determine rates and direction of growth, the endocrine balances are perhaps the most conspicuous. Variations in body build also involve differences in the mechanical stresses and strains imposed upon articular structures. In the sthenic individual a greater weight is supported by the joint structures than is supported by the weight-bearing tissues of the asthenic individual. It is recognized that congenital defects and anomalies occur in various organs and tissues as a resultant of endocrine dysfunction, and there is no way of disproving the possibility that moderately defective cartilage might not seem inadequate until the sum of total wear and tear exceeds the limits of this structure to withstand disintegration. Furthermore, a defective structure might break down early or later in life, depending upon the adequacy of its nutritive pabulum. The vascular supply to the region, the lymphatic drainage of the area, together with the intercellular communicating spaces, all play a rôle in determining the survival period of tissue. The effective supply of nutrients to articular regions is dynamically influenced by nervous and endocrine factors as well as by the anatomical integrity of the blood vessels. Vasomotor instability in the arthritic, already mentioned in connection with the symptoms of cold, clammy hands, may have still more deep-seated consequences. Vasomotor instability, although involving a variety of factors, may be reasonably

referred to dysfunction of the neuroendocrine system. This hereditary or congenital aspect of the matter is only one phase of the problem, however.

In addition to these features of rheumatic disease, a comparison of symptoms in experimental animals, subjected to deficiencies or excesses of pituitary factors, lends circumstantial evidence regarding the potential importance of the pituitary in relation to rheumatic disease. A general parallelism of symptoms between rheumatic patients and experimental animals subjected to hypophysectomy suggests that a common factor underlies both. The loss of the factor regulating protein metabolism following hypophysectomy in adult rats decreases the level of serum albumin and increases the level of serum globulin.[24] As noted earlier in this discussion, a corresponding deviation of serum albumin and globulin characterizes many patients with severe rheumatic disease. The changes just referred to in hypophysectomized rats show that the rise in the globulin fraction characteristic of the formation of antibodies such as develop during infection is probably not the simple humoral reaction which it has seemed to be, but is probably mediated through a central control mechanism. Although infection has been generally credited with producing this deviation as a direct response in the arthritic, it is equally conceivable that infection achieves this deviation secondarily by way of a primary influence upon the central defense mechanism of which the pituitary and associated endocrine system are a part. The rheumatic subject is abnormally sensitive to stresses of heat, cold, exercise, trauma and infections. Animals deprived of the pituitary gland are likewise in a meta-stable state [23] and respond poorly to heat, cold, exercise, trauma, infections and toxins. Asthenia is common to both the arthritic and the hypophysectomized animal.

It is not widely recognized that in addition to the local influences exerted by microörganisms upon tissues of the body per se, the presence of colonies of bacteria must divert nutrient substances from the support of essential structures. In this respect focal infection acts as a "parasitic growth," thereby producing a drain upon the nutritive resources of the host. Focal infection may indeed sometimes exercise its influences less by invasion than by extraction. The defensive reactions upon the part of the body such as leukocytosis, and the formation of humoral antibodies, involve dislocations and readjustments in body economy. The price of maintaining defense against infection is a physiological cost expressable in terms of lesser amounts of materials available for maintenance of tissues, even to the point of insufficiency. In the demands thus made, the whole chain of defense is involved. Certain of these links, however, should be considered more closely because of the recognized control which they exercise upon others. Thus, a functional insufficiency of pituitary hormones induced either by exhaustion or by direct stimulus might conceivably be comparable in its effect to anatomic absence of the gland. It appears that a part of the influence of the pituitary may be effected by way of the adrenal cortex, inasmuch as desoxycorti-

costerone prevents the change in serum proteins associated with hypophysectomy.

Other features of the rheumatic syndrome which may be attributed to a deficiency of either the adrenotropic hormone of the pituitary or the cortical hormones of the adrenal include fatigue, hypotension and lowered metabolic rate. Fatigue is conspicuous in nearly all rheumatics. Hypotension and decreased metabolic rates appear in approximately one-third of the patients in most large series of cases. Deficiency of the adrenocortical hormone might arise from hereditary insufficiency or as a secondary response to infection, toxemia or other physiological "drafts." Similarly, relative insufficiency of the thyrotropic hormone may give rise to certain of these symptoms, particularly the lowered basal metabolic rate (−15–20) and the elevated cholesterol (in hypertrophic arthritis). Cases presenting these symptoms are often benefited by appropriate doses of desiccated thyroid.[25, 26, 27, 28, 29, 30]

In contrast, Duncan [31] has described patients with articular distress associated with hyperthyroidism who have been benefited by thyroidectomy. While these data appear contradictory, this conflict may be more apparent than real. The articular manifestations may be regarded as resultants of either hyper- or hypoactivity of the thyrotropic portion of the pituitary. This situation does not represent a special case but is a general biologic function. States of dysfunction often follow successive periods of greater or lesser activity. This phasic response is well recognized in respect to the circulatory system and is also appreciated by endocrinologists.

The most direct evidence regarding the importance of the rôle of the pituitary and other endocrines in rheumatic disorders appears in women. This evidence appears in three general categories, viz., in respect to (1) the menstrual cycle, (2) pregnancy, and (3) the climacteric.

Patients with arthritis nearly always experience an exacerbation of symptoms a short time preceding the onset of menstrual flow. It appears likely that this is related to the water retention [12] occurring at this period. Underlying this, however, is the changing hormonal balance.

Chronic arthritics frequently experience a remission of active symptoms during pregnancy. This relief is so definite that Hench [32] has described patients with atrophic or rheumatoid arthritis who have become pregnant for "therapeutic purposes." One case of arthritis is on record in which a woman underwent nine pregnancies, experiencing relief in the course of each one.[32a] The metabolic activities of the pregnant woman are profoundly different from those of the non-pregnant. Endocrinous and hormonal factors are controlling elements in the situation.

Finally, a considerable number of women develop arthritic symptoms at the time of the climacteric. This occurs so frequently that a special class of rheumatic disease, designated as menopausal arthralgia, is widely recognized.[33, 34, 35] This symptom-complex may appear not only with the natural menopause but also following castration. The arthritic symptoms are often improved by the administration of estrogens. The favorable influence of

estrogens is probably not direct, but secondary to the relative depression of pituitary hormone production brought about by the estrogenic substances. Increased excretion of pituitary hormones appears following castration and the coarsening of features appearing at this time may reflect the systemic influences of increased growth factors. In illustration of this, one atrophic arthritic of 15 years' duration achieved symptomatic and longstanding arrest of a widespread symmetrical process but shortly before death developed facial symptoms suggestive of acromegaly. Osgood[34] has related the symptoms of menopausal arthritis to an increased level of pituitary substances, incidental to depletion of estrogens. Pursuing the same line of reasoning, irradiation of the pituitary has been suggested as a therapeutic measure. The principal pathologic feature of menopausal arthralgia, according to Osgood, is synovitis or degenerative joint change or both. In addition to this, Albright[36] et al. have called attention to a postmenopausal osteoporosis. This is seen in the spine and pelvis and is apparently due to failure of osteoblasts to lay down adequate organic matrix. Another pathologic feature associated with the menopause bearing upon rheumatic symptoms has been described by Kling,[37] viz., juxta-articular adiposis dolorosa with painful masses of fat near the joints. Whether this stems from pituitary dysfunction has not been demonstrated, but it appears probable in view of the similar fat dystrophy occurring in cases of pituitary disease.

Direct evidence has been presented that pituitary substances influence the growth of cartilage. Osteophytes have been produced by pituitary extracts in the spinal ligaments of dogs which are indistinguishable from those associated with degenerative (hypertrophic) joint disease.[38] Silberberg[39] has noted fibrillation of the articular cartilage of guinea pigs subjected to repeated injections of an acid extract of the anterior pituitary gland of cattle. Clinical states of acromegaly are often associated with articular lesions which bear a gross resemblance to those of hypertrophic arthritis. In addition to the articular osteophytes, splanchnomegaly or enlargement of visceral organs, together with paresthesia, occur in acromegaly. These non-articular symptoms are also presented by a number of arthritics.

In addition to symptoms referable to dysfunction of the anterior pituitary there are certain extra-articular symptoms of rheumatism which may be referable to dysfunction of the posterior pituitary. The tendency of the arthritic toward the development of a low-grade peripheral edema, described earlier in this text, may be attributed to excessive secretion of the pitressin fraction, i.e., the antidiuretic substance of the post-pituitary as well as of the gonadotropic fraction of the anterior portion of the pituitary.

Therapeutic application of the implications inherent in the foregoing considerations have been given limited but by no means complete trials. Lichtwitz[40] has advanced the view that arthritis originates from a disorder of the hypothalamic pituitary complex. Estrogens have been extensively employed in the treatment of menopausal arthralgia. Androgens have been used only occasionally in attempts to control atrophic spondylitis.[41] Some

efforts have been made to depress the growth functions of pituitary activity by the roentgen-ray. Thyroid has been used in hypothyroid and thyroidectomy in hyperthyroid arthritics with benefit not only to the thyroid condition but to the articular symptoms as well. Freyberg [42] has recently summarized a series of observations indicating limitations of hormone therapy.

In an attempt to bring the foregoing varied and numerous considerations to some sort of visual focus, however imperfect, certain of the symptoms appearing among arthritics which have counterparts in specific states of endocrine hypo- or hyperactivity are summarized in table 1. Some symptoms

TABLE I

Possible Rôle of Precipitating Factors, Acting Singly or in Combination, in Producing Symptoms of Chronic Rheumatic Disorders Through the Mediation of "Central Factors"

Precipitating or Sustaining Factors	Affecting Relative Functional Levels of Neuro-Endocrine System	Symptom Complex Resulting in the Arthritic	Type of Arthritis Involved
Infection, toxemia, hereditary imbalance, physiological "draft"; "starvation"; vitamin B complex deficiency	*Hypo* function of the *adrenotropic* factor of the pituitary or	Increased susceptibility to infection, toxins, histamine	A & H
	Adrenal cortex	Caries	A & H
		Fatigue	A & H
		Asthenia	A
		Hypotension	A
		Low BMR	A & H
	Hypo function of the *growth* factor of the pituitary	Asthenic (small stature)	A
		Secondary anemia	
		Decreasing capacity for protein synthesis	A & H
		Demineralization	A
	Hyper function of the *growth* factor of the pituitary	Osteophytes	H
		Calcification of cartilage	H
		Acral enlargement	H
		Paresthesia	
		Megacolon	H
		Sthenic (large stature)	H
Menopause	*Hypo* function of the *thyrotropic* factor of the pituitary or	"Dry" skin	H
		Low BMR	A & H
	Thyroid		
	Hyper function of the *thyrotropic* factor of the pituitary or	High BMR	
	Thyroid		
	Hypo function of the *gonadotropic* factor of the pituitary or	Arthralgia	A & H
		"Flashes"	
	the gonads	Fatigue	
		Sweating	
		Vasomotor	
		Emotional instability	
		Headache	
		Hypertension	

TABLE I—*Continued*

Precipitating or Sustaining Factors	Affecting Relative Functional Levels of Neuro-Endocrine System	Symptom Complex Resulting in the Arthritic	Type of Arthritis Involved
Pregnancy	*Hyper* function of the *gonadotropic* factor of the pituitary or Gonads	Relief of symptoms	A
	Hypo vasopressor factor of the posterior pituitary	Decreased peristalsis Low blood pressure	A & H
	Hyper-vasopressor factor of the posterior pituitary	Water retention Edema Decreased skin capillary flow	
	Nervous System		
Mechanical pressure by capsular distention, bony overgrowth, tissue swelling	Pain fibers	Pain	A & H

Nervous stress or strain from: worry, excessive activity, exposure to cold—trauma	Vegetative nervous system
	
	(1) Stimulation followed by
	(2) Exhaustion
	
	   (a) Increased adrenergic response (Epinephrine)
	
	   (b) Increased cholinergic response (Acetylcholine)
		
		Peripheral vasoconstrictions
		Hyperglycemia
		Relaxation gastrointestinal tract
		
		Increased gastrointestinal tone
		Flushing
		Palpitation
		Sweating—general
			A & H

Exhaustion	Decreased adrenergic response	Reduced resistance to fatigue—cold Decreased BMR Poor regulation body temperature	A

are referred to imbalance in the central and in the vegetative nervous systems as well as to endocrinous factors. The separation of the vegetative nervous system from the endocrine chain may appear artificial inasmuch as these are functionally integrated. However, such a division may partially clarify the rôle of these several central factors in the pathogenesis of the multiplicity of symptoms characterizing arthritis.

Stimuli or factors such as heredity, physical activity, nutritive defects, infection, trauma and exposure may be conceived as impinging on a central mechanism. The factors comprising this mechanism are the great systems of the body, interrelated, as they are known to be, through the central nervous and endocrine chains. Many of the objective phenomena of the rheumatoid syndrome can be seen to consist of phenomena which reflect, to some extent,

supposedly normal activities of the systems concerned. It is, therefore, tempting to endeavor to relate some of these phenomena, as exhibited in disease, to under- or overaction of the systems or organs having comparable or parallel functions. No attempt to this end could be regarded with finality but it is rather surprising to observe the extent to which such an hypothesis affords a working explanation of many otherwise apparently unrelated symptoms. The symptom-complex constituting rheumatic disease, regarded in this manner, may perhaps be better described as a mesodermosis. This avoids the view that arthritis is a disorder in a single tissue produced by a solitary etiologic factor and hence amenable to a single therapeutic agent.

Development of the above hypothesis makes possible at least a tentative explanation of the alleged value of a large variety of therapeutic agents which seem to have little in common and yet, at times at least, achieve beneficial results. Under this heading can be grouped various forms of vaccines in many of which it is clear that there is no true specificity. Also to be included are such agencies as Coley's fluid, non-specific protein, bee-venom, snake-venom, typhoid injections, possibly sulphur, and also that agent which is now uppermost in the medical mind, namely, gold. The statement has been frequently made that almost any vigorous measure which is brought to bear on the arthritic, including injection of foreign substances, may achieve benefit. The injection of all of these agents induces, by definition, a greater or less defense reaction on the part of the host which may or may not express itself locally at the site of the injection. Whether or not any local antigenic reactions are developed there also takes place, by definition, a stimulation of the defense mechanism of the body as a whole in which are involved the central nervous and endocrine systems in the sense discussed above. This is perhaps most typically to be seen in the injection of typhoid vaccine in doses sufficient to induce marked fever. In such a case it is reasonable to believe that there take place so-called overflow reactions, the nature of which is in no sense specific but expresses itself widely throughout the economy. The fever is simply an end expression of the reaction and indicates the extremity to which the measure has been pushed. Less vigorous exhibitions of the same principle which do not provoke fever may, nevertheless, initiate the same general chain of defense mechanisms. Only through enlistment of central reactions can the benefits resulting from such a series of injections as is above detailed, be explained.

SUMMARY

A survey of the clinical patterns of rheumatic disease reveals that the disorder not only affects the anatomy of articular structures but involves the functional integrity of the nervous, respiratory, neurovascular, muscular and gastrointestinal systems as well. The blood of the arthritic also presents abnormalities of its cellular and fluid components. Etiologic and sustaining factors, including infectious, traumatic, and nutritive influences, are varied

and numerous. Susceptibility of individuals to the development of rheumatic disease is greater in certain families than in others and varies with body build. These several facts may be correlated by considering the symptoms of rheumatic diseases, at least rheumatoid (atrophic) and osteo (hypertrophic) arthritis, as, primarily, direct consequences of disturbance in the several functions of the neuro-endocrine system as a whole and especially those of the pituitary gland. These disturbances of the pituitary may be determined either by congenital inadequacy or by excessive stimulation with subsequent periods of functional hyperactivity or hypoactivity. It appears unlikely that any single factor is responsible for producing the full pattern in any case.

The influences of the pituitary are perhaps most clearly operative in the so-called menopausal arthritis. The exacerbation of symptoms of stiffness and pain in an arthritic during the premenstrual phase of the reproductive cycle, and the remission of rheumatic complaints during pregnancy, although more immediately referable to gonadal activities, involve pituitary activities as well. Similarly arthralgic manifestations associated with hypothyroidism may involve pituitary factors. The states of fatigue and general asthenia characterizing many chronic arthritics could be attributed to adrenocortical insufficiency secondary to dysfunction of the pituitary. Circulatory and thermo-regulatory disturbances, seen in many arthritics and involving imbalance of the nervous system, may likewise depend upon endocrine influences initiated in the pituitary organ. Certain of the skeletal and cartilaginous defects characterizing rheumatic diseases are seen in cases of frank endocrine disease and some have been produced by pituitary substances in experimental animals.

These considerations, in addition to their theoretical interest in accounting for the symmetrical distribution of lesions and certain systemic dysfunctions, bear suggestive therapeutic corollaries which have not yet been fully explored and invite clinical as well as experimental exploitation. Nothing approaching finality of detail is here implied or intended but it is abundantly clear that any attempt at visualization of the arthritic problem as a whole must include in its purview the broad outline of the considerations here presented.

BIBLIOGRAPHY

1. PEMBERTON, R.: The nature of arthritis and rheumatoid conditions, Jr. Am. Med. Assoc., 1920, lxxv, 1759.

2. KEY, J. A.: Personal futile attempts to prove infectious origin of chronic arthritis, South. Med. Jr., 1933, xxvi, 1059.

3. ANGEVINE, D. M., ROTHBARD, S., and CECIL, R. L.: Cultural studies on rheumatoid arthritis and rheumatic fever, Proc. Am. Rheum. Assoc., Jr. Am. Med. Assoc., 1940, cxv, 2112.

4. SABIN, A. B., and JOHNSON, B.: Search for micro-organisms of the pleuropneumonia group in rheumatic and non-rheumatic children, Proc. Soc. Exper. Biol. and Med., 1940, xliv, 565.

5. HENCH, P. S.: Is rheumatoid (atrophic) arthritis a disease of microbic origin? A summary of arguments for and against the infectious theory; a survey of chronic rheumatic diseases, 1938, 35, Oxford University Press, London.

6. BAUER, W.: Studies pertaining to the origin and nature of hypertrophic arthritis, Trans. and Stud. Coll. Phys. Philadelphia, 1939, vii, 1.

7. FARRAR, G. E., and RAYBURN, F. W.: The blood in arthritis, Med. Clin. N. Am., 1940, xxiv, 1633.

8. RACE, J.: Laboratory findings in rheumatic diseases, Jr. State Med., 1937, xlv, 258.

9. DAWSON, M. H., and OLMSTEAD, M.: Agglutination and precipitin reactions in rheumatoid arthritis with hemolytic streptococci, Groups A and G, Proc. Soc. Exper. Biol. and Med., 1936, xxxiv, 80.

10. DAVIS, J. S., JR.: Protein studies in atrophic (rheumatoid) and hypertrophic arthritis, Jr. Lab. and Clin. Med., 1936, xxi, 478.

11. SCULL, C. W., BACH, T. F., and PEMBERTON, R.: Serum proteins in rheumatoid disease, ANN. INT. MED., 1939, xii, 1463.

12. SCULL, C. W., and PEMBERTON, R.: The influence of dietetic and other factors in the swelling of tissues in arthritis, ANN. INT. MED., 1935, viii, 1247.

13. JACOBSON, S. D., LEICHTENTRITT, B., and LYONS, R. H.: The effect of acid and alkaline salts on some patients with rheumatoid arthritis, Am. Jr. Med. Sci., 1942, cciv, 540.

14. HARTUNG, E. F., and STEINBROCKER, O.: Gastric acidity in chronic arthritis, ANN. INT. MED., 1935, ix, 252.

15. RAWLS, W. B., WEISS, S., and COLLINS, V. L.: Liver function in rheumatoid (chronic infectious) arthritis, ANN. INT. MED., 1939, xii, 1455.

16. WILLARD, J. H., and STRAWBRIDGE, R. R.: Gall bladder infection as a factor in arthritis, Med. Clin. N. Am., 1940, xxiv, 1709.

17. SPACKMAN, E. W., BACH, T. F., SCULL, C. W., and PEMBERTON, R.: Complete roentgenray studies of the gastro-intestinal tract in 400 arthritics, Am. Jr. Med. Sci., 1941, ccii, 68.

18. PEIRCE, E. G., cited by PEMBERTON, R., and SCULL, C. W.: The circulation in chronic arthritis in "A survey of chronic rheumatic diseases," 107, 1938, Oxford University Press, London.

19. WRIGHT, L. M., and PEMBERTON, R.: The peripheral surface temperature in arthritis, Arch. Int. Med., 1930, xlv, 147.

20. STECKER, R. M.: Heberden's nodes; heredity in hypertrophic arthritis of the fingers, Proc. Am. Rheum. Assoc., Jr. Am. Med. Assoc., 1940, cxv, 2024.

21. PEMBERTON, R., and PEIRCE, E. G.: A clinical and statistical study of chronic arthritis based on eleven hundred cases, Am. Jr. Med. Sci., 1927, clxxiii, 31.

22. WILSON, M. G., and SCHWEITZER, M. D.: Rheumatic fever as a familial disease: environment, communicability and heredity in their relation to the observed familial incidence of the disease, Jr. Clin. Invest., 1937, xvi, 555.

23. SWANN, H. G.: The pituitary adreno-cortical relationship, Physiol. Rev., 1940, xx, 493.

24. LEVIN, L., and LEATHEM, J. H.: Relation of hypophysis and the adrenal cortex to serum protein metabolism, Jr. Biol. Chem., 1941, lxxvi, 140.

25. CECIL, R. L., BARR, D. P., and DUBOIS, E. F.: Clinical calorimetry 31, observations on the metabolism of arthritis, Arch. Int. Med., 1922, xxix, 583.

26. PEMBERTON, R., and TOMPKINS, E. H.: Studies on arthritis in the Army, based on 400 cases: Observations on basal metabolism, Arch. Int. Med., 1920, xxv, 231.

27. SWAIM, L. T., and SPEAR, L. M.: Studies of basal metabolism in chronic arthritis, Boston Med. and Surg. Jr., 1927, cxcvii, 350.

28. RAWLS, W. B., RESSA, A. A., GRUSKIN, B., and GORDON, A. S.: Thyroid activity in chronic arthritis, ANN. INT. MED., 1938, xi, 1401.

29. HALL, F. C., and MONROE, R. T.: Thyroid gland deficiency in chronic arthritis, Jr. Lab. and Clin. Med., 1933, xviii, 439.

30. DUNN, C. W.: Present status of endocrine therapy in arthritis, Med. Clin. N. Am., 1940, xxiv, 1697.
31. DUNCAN, W. S.: The relationship of thyroid disease to chronic non-specific arthritis, Jr. Am. Med. Assoc., 1932, xcix, 1239.
32. HENCH, P. S.: The ameliorating effect of pregnancy on chronic atrophic (infectious rheumatoid) arthritis, fibrositis, and intermittent hydrarthrosis, Proc. Staff Meet. Mayo Clin., 1938, xiii, 161–167.
32a. Queries and minor notes: Arthritis subsiding during pregnancy, Jr. Am. Med. Assoc., 1937, cix, 2161.
33. CECIL, R. L., and ARCHER, B. H.: Classification and treatment of chronic arthritis, Jr. Am. Med. Assoc., 1926, lxxxvii, 741.
34. a OSGOOD, R. B.: The medical and social approaches to the problem of chronic rheumatism, Am. Jr. Med. Sci., 1940, xx, 429.
    b OSGOOD, R. B.: (loc. cit.)
35. HALL, F. C.: Menopause arthralgia; a study of twenty-one women at artificial menopause, New England Jr. Med., 1938, ccxix, 1015.
36. ALBRIGHT, F., BLOOMBERG, E., and SMITH, P. H.: Post menopausal osteoporosis, Trans. Assoc. Am. Phys., 1940, lv, 298.
37. KLING, D. H.: Juxta-articular adiposis dolorosa: its significance and relation to Dercum's disease and osteo-arthritis, Arch. Surg., 1937, xxxiv, 599.
38. PUTNAM, T. J., BENEDICT, E. B., and TEEL, H. M.: Studies in acromegaly: experimental canine acromegaly produced by injections of anterior lobe pituitary extract, Arch. Surg., 1929, xviii, 1708.
39. SILBERBERG, M., and SILBERBERG, R.: Effects of endocrines on age changes in the epiphyseal and articular cartilages, Endocrinology, 1942, xxxi, 410.
40. LICHTWITZ, L.: Functional pathology, 1941, Grune and Stratton, Inc., New York, p. 10.
41. AUB, J. C.: Endocrines: use of testosterone, New England Jr. Med., 1940, ccxxii, 877.
42. FREYBERG, R. H.: Treatment of arthritis with vitamins and endocrine preparations, Jr. Am. Med. Assoc., 1942, cxix, 1165.

CASE REPORTS

SUPERIOR AND INFERIOR VENAE CAVAE THROMBOSIS WITH POLYCYTHEMIA; REPORT OF A CASE *

By Oscar B. Ragins, M.D., and George C. Coe, M.D., *Chicago, Illinois*

Thrombosis of the superior vena cava is an unusual condition, but thrombosis of both the superior and inferior venae cavae is indeed rare. In an exhaustive review of the literature in 1936 Ochsner and Dixon[1] collected 120 cases of superior vena cava thrombosis and added two of their own. Subsequently, individual cases have been reported by Szour and Berman,[2] Blasingame,[3] Buzzard,[4] and Rutledge and Gray.[5] In none of these, however, is any reference made to both superior and inferior venae cavae thrombosis.

We wish to report such a case, diagnosed antemortem and proved at autopsy, with several unusual findings not reported in other cases that warrant discussion.

CASE REPORT

The patient, a white male, aged 42, entered the Cook County Hospital on September 9, 1940 complaining of pain in the left groin of several months' duration. He had been a moderate alcoholic for years. Physical examination revealed a left-sided inguinal hernia and a left undescended testicle. The face presented a ruddy cyanosis, and varicose veins were evident on both legs. Temperature, pulse and respiration were normal, and the blood pressure was 106 mm. Hg systolic and 90 mm. diastolic. Laboratory findings were hemoglobin 85 per cent, red cells 4,900,000 and white cells 8100. Urinalysis was negative.

Operation for the hernia and undescended testicle was performed on September 13, 1940. On the twelfth postoperative day, a large hematoma was noted at the site of the inguinal incision and on the twentieth postoperative day the base of the wound became necrotic and secondarily infected. His temperature rose to 101.2° F., and examination revealed a distended abdomen with shifting dullness. The spleen was palpable at the costal margin.

The patient was transferred to our medical service for diagnostic study on the sixty-sixth postoperative day. At this time physical examination revealed a diffuse florid cyanosis of the face, most marked in recumbency, with a peculiar puffiness of the face, especially on the right side. The superficial neck veins and the veins of the upper extremities, especially the right, were markedly distended. Varicosities of the veins of the anterior chest wall and shoulders were evident. There was also dilatation of the cutaneous venous capillaries along the right costal arch and slight edema of the right anterior chest wall and right shoulder. Heart and lungs appeared essentially normal. The abdomen was distended and there was evidence of ascites. The spleen was enlarged, being palpable about three fingers below the costal arch, and the veins on the lateral surface of the abdomen were dilated. Blood pressure was 110 mm. Hg systolic and 70 mm. diastolic, and there was slight pitting edema also of the lower extremities.
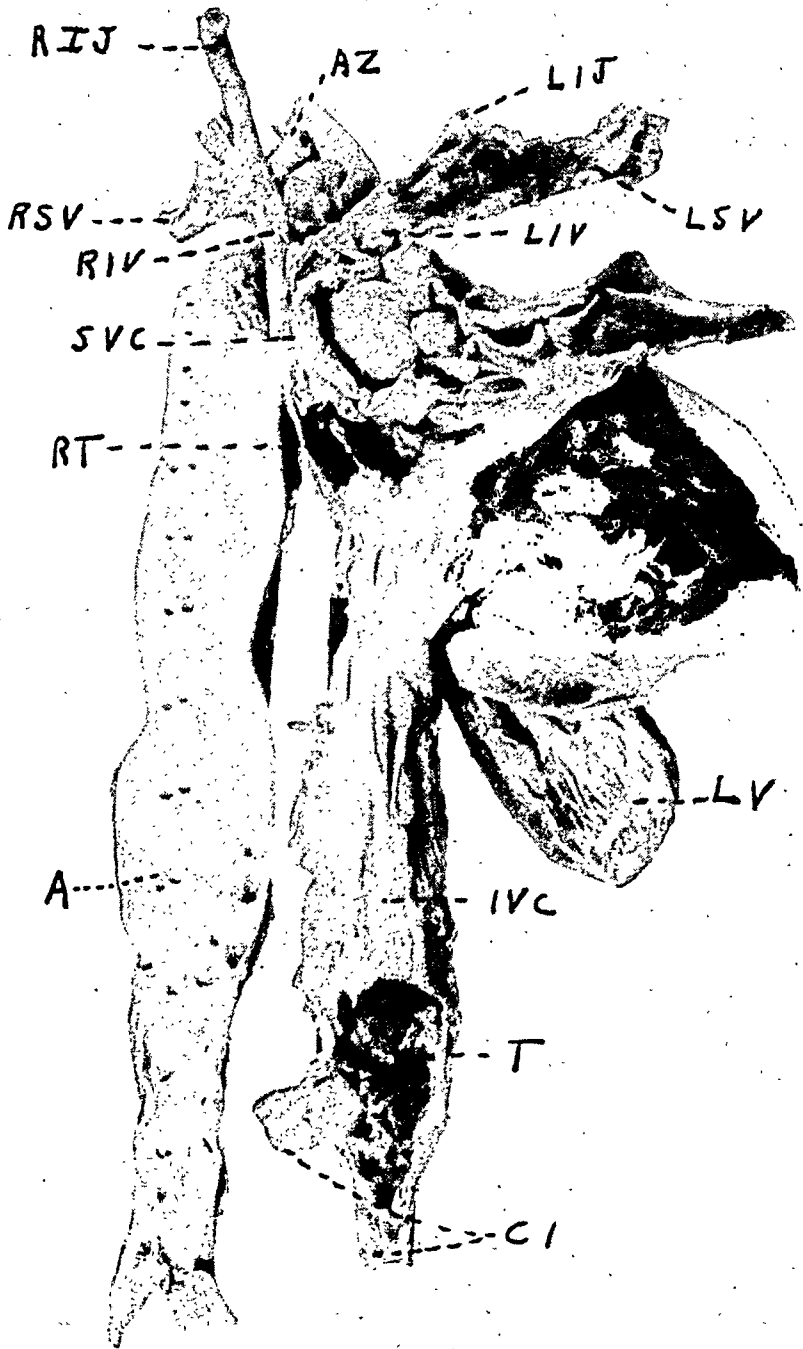
FIG. 1. A—Aorta. IVC—Inferior vena cava. LV—Left ventricle with marked fibrosis and thinning of the wall. T—Thrombus in the inferior vena cava. CI—Common iliac veins. SVC—Superior vena cava. RIV—Right innominate vein. LIV—Left innominate vein. RSV—Right subclavian vein. LSV—Left subclavian vein. RIJ—Right internal jugular vein. LIJ—Left internal jugular vein. AZ—Azygos vein. RT—Thrombus of the superior vena cava extending into the right auricle.

Studies of the peripheral blood for the first time revealed a polycythemia. Hemoglobin values varied between 98 and 100 per cent, red cell counts between 5,940,000 and 6,250,000 and white cell counts between 15,000 and 30,250 with essentially normal differential counts. A bone marrow study was essentially normal. Roentgenographic examination of the chest was negative, removing the possibility of some mediastinal mass constricting the superior vena cava, and a barium meal revealed the presence of esophageal varices. Blood chemistry studies (total protein, albumin, globulin, phosphorus, phosphatase, nonprotein nitrogen, creatinine, uric acid, etc.), although not entirely within normal ranges, were not significant. Stool specimens were positive for blood.

The patient was permitted to go home at his own request and our diagnosis at this time was superior (and inferior) venae cavae obstruction, possibly thrombosis, and secondary polycythemia with splenomegaly. Although the etiology was not certain, we felt that it was associated in some manner with the postoperative wound infection and an extensive thrombophlebitic process.

The patient returned 11 days later complaining of marked swelling of the abdomen and legs. Physical examination revealed an acutely ill and dyspneic patient with intense ruddy facial cyanosis. The superficial veins of the neck and chest wall, particularly on the right side, were markedly engorged, as were also the veins of the abdominal wall. The right side of the face and neck, the upper right arm, the right side of the chest and abdominal wall and the lower extremities revealed pitting edema. The lungs were resonant except at the bases, the heart normal, the spleen palpable, the abdomen more distended, and ascites more pronounced. The blood pressure for the first time was elevated, being 150 mm. Hg systolic and 100 mm. diastolic.

The blood count showed hemoglobin 100 per cent, red cells 7,960,000 and white cells 39,200, with 97 per cent polymorphonuclear leukocytes, 1 per cent lymphocytes, 1 per cent eosinophiles and 1 per cent basophiles, with some poikilocytosis and polychromatophilia. Blood platelets were increased.

Abdominal paracentesis yielded 8000 c.c. of a milky fluid with a specific gravity of 1.013, a 2 + protein content and 130 red and 80 white cells per cu. mm. Four days later he developed some hemoptysis and became very cyanotic and dyspneic, but was relieved by venesection of 400 c.c. blood and a second abdominal paracentesis of 7000 c.c. of a similar milky fluid.

Roentgenographic examination of the chest now revealed some encapsulated fluid in the right thorax. Repeated blood counts continued to show the picture of polycythemia and stools continually showed the presence of blood. Total blood proteins, albumin and globulin were normal; blood phosphorus was slightly increased and phosphatase activity markedly increased (11.94 units); non-protein nitrogen and icteric index were also increased.

On January 31, 1941 the patient suddenly became intensely cyanotic and dyspneic and died.

Essential Autopsy Findings. The autopsy was performed by Dr. William Mavrilus. The conjunctivae, mucosa of the lips and mouth, and the skin of the entire body, especially that of the upper extremities, head and neck, and the finger and toe nails were deeply cyanotic. The blood vessels of the neck were distended and engorged. There was pitting edema of the neck, chest, upper abdomen and upper portion of the lower extremities. The abdomen was distended two fingers above the level of the thorax. The subcutaneous tissues, especially in the neck, chest and upper abdomen, were edematous.

The abdominal cavity contained about 6500 c.c. of a light tan turbid fluid. The liver extended 2 cm. below the xiphoid process and the lower pole of the spleen was at the left costal margin at the posterior axillary line. The left pleural cavity contained 1500 c.c. of a light turbid fluid similar to that present in the abdominal cavity

and the right pleural cavity contained 1000 c.c. with focal fibrous adhesions at the lower lobe and diaphragm.

The superior vena cava was completely occluded by an organized thrombus adherent to the intima and endocardium which extended for about 3 cm. into the right auricle, upward into the right and left innominate veins and subsequently into the right and left internal jugular veins, the right and left subclavian veins and into the azygos vein. From the right auricle it extended into the right internal jugular vein for a distance of 17 cm. and into the left internal jugular vein for 8 cm. Beyond the thrombus in the left subclavian and left internal jugular veins the lumina were dilated. The adventitial tissue about the greater veins was firmly adherent to the perivascular tissue. The thrombus in the left greater vein was loosely adherent and more fibrinous than that in the right (figure 1).

Fig. 2. Muscle and perivascular tissue of the inferior vena cava showing marked polymorphonuclear and round cell infiltration.

In the inferior vena cava about 5 cm. above the bifurcation of the common iliac veins, a purplish red thrombus, firmly attached to the intima, completely occluded the lumen. This thrombus extended upward for a distance of 5 cm., and there was a partial occlusion by a small thrombus extending downward into the left common iliac vein. Above the point of the complete occlusion the inferior vena cava was moderately dilated.

Microscopic Lesions. The superior vena cava was completely occluded by a well organized thrombus composed of collagenous fibrous tissue with round cell and polymorphonuclear infiltration, the round cells predominating. There were numerous recanalized vessels through the organized thrombus filled with erythrocytes and few leukocytes. Moderate round cell infiltration with occasional polymorpho-

nuclears was present in the media and adventitia, especially around the interstitial vessels. A similar condition was found in the right innominate, right subclavian, right internal jugular and azygos veins.

The left subclavian vein showed moderate edema of all the layers of its wall with round cell and polymorphonuclear infiltration, especially about the interstitial vessels. In the adventitia was dense infiltration of polymorphonuclear and few round cells, extending into the perivascular tissue. The lumen was partially filled with erythrocytes and leukocytes and macrophages filled with hemosiderin pigment granules.

The layers of the wall of the inferior vena cava were markedly edematous, and the interstitial blood vessels and capillaries were dilated and congested. Moderate round cell and polymorphonuclear infiltration was evident in the wall, especially around the interstitial vessels. A large thrombus, composed of fibrous tissue strands, erythrocytes, leukocytes, fibrin and platelets, was attached to the intima by newly formed capillaries and fibroblasts. The organized portion of the thrombus was infiltrated by many round and polymorphonuclear cells. This was also evident in the muscle and perivascular tissue about the inferior vena cava, especially about the small and large blood vessels (figure 2).

DISCUSSION

We believe that the etiology of the extensive thrombotic process in this patient was the marked phlebitis with vascular and perivascular cellular infiltration, the polycythemia most probably being caused by the anoxemia which resulted from the extensive venous obstruction and pulmonary congestion.

In the cases reviewed by Ochsner and Dixon, the thrombosis resulted from phlebitis in 36.6 per cent of cases, from external compression in 29.1 per cent, and from mediastinitis in 23.3 per cent. The cause was unknown in 10.8 per cent. Of the 44 cases (36.6 per cent) resulting from phlebitis, 20 were idiopathic, 12 had syphilitic phlebitis, four tuberculous phlebitis, seven pyogenic phlebitis and one thrombotic phlebitis. Of the 20 idiopathic cases, 10 had associated heart disease. Unfortunately, these and the other reported cases give no information with regard to blood counts so that the presence or absence of a secondary polycythemia cannot be determined.

The clinical manifestations of superior vena cava thrombosis are caused by the stasis of blood in the venous tributaries draining into the superior vena cava and are limited, therefore, to the upper part of the body. This causes an increase in venous pressure in the upper half of the body and edema (due to transudation) but since collateral circulation develops, pitting generally does not occur. In our patient it did occur because of the associated thrombosis of the vessels draining into the superior vena cava. Livid cyanosis, especially of the face, results from the anoxemia due to blood stagnation, and dyspnea develops because of the slowing of local circulation with accumulation of CO_2 in the blood. Compression of the vena azygos major causes a hydrothorax and edema of the chest wall with prominence of the superficial veins due to venous stasis and increased pressure, and although this may occur bilaterally, it is generally unilateral involving the right side. The edema and cyanosis are generally increased when the patient assumes the horizontal posture. Cough is an early symptom and cerebral symptoms, such as headache, vertigo, somnolence, etc., are not uncommon because of stasis in the cerebral vessels.

If, in addition to obstruction of the superior vena cava, the inferior vena cava becomes obstructed, as occurred in our case, the lower portions of the body

become edematous and the veins distended. Thus, in our patient ascites, and edema of the abdominal wall and lower extremities were evident as well as prominence of the veins of the abdominal wall.

In the series reported by Ochsner and Dixon the mortality in the phlebitis group was 72.7 per cent. If the patient lives long enough, adequate collateral circulation may develop. This is evident in the case reported by Blasingame who observed this condition in a cadaver. The patient was a while male, aged 93, who died from cardiorenal disease and who presented no surface indications of increased venous distention. Careful dissection revealed complete thrombotic occlusion of the superior vena cava and innominate vein with partial occlusion of the subclavian and internal jugular veins and with establishment of adequate collateral circulation. Thus, the whole process appeared of long standing and was not the immediate cause of death.

In the case reported by Rutledge and Gray, the patient, male, aged 37, was operated on and the thrombus was located within the superior vena cava with a constricting band on the outside. The band (either inflammatory or congenital in origin) was cut and the thrombus was not disturbed. The patient improved after surgery and up to the time of this report was doing well. Conceivably, the thrombus became canalized. This case indicates the importance of etiologic diagnosis of superior vena cava obstruction.

SUMMARY

An unusual case of both superior and inferior venae cavae thrombosis, diagnosed antemortem and confirmed at autopsy, is reported. The etiology of the extensive thromboses in this case was most likely the postoperative phlebitis and vascular and perivascular infiltration. The associated polycythemia was a physiological secondary polycythemia due to venous stasis and anoxemia.

BIBLIOGRAPHY

1. OCHSNER, A., and DIXON, L. J.: Superior vena caval thrombosis; review of literature and report of cases of traumatic and infectious origin, Jr. Thorac. Surg., 1936, v, 641–672.
2. SZOUR, M., and BERMAN, R.: Thrombosis of superior vena cava in pulmonary tuberculosis; case, Rev. de la tuberc., 1936, ii, 1068–1075.
3. BLASINGAME, F. J. L.: Occlusion of the superior vena cava and its tributaries, associated with established collateral circulation, Arch. Path., 1938, xxv, 361–364.
4. BUZZARD, E. M.: Thrombosis of superior vena cava, Brit. Jr. Tuberc., 1940, xxxiv, 39–44.
5. RUTLEDGE, D. I., and GRAY, H. K.: Indeterminate type of obstruction of the superior vena cava, Proc. Staff Meet. Mayo Clin., 1939, xiv, 337–340.

HEMOCHROMATOSIS; A CASE REPORT WITH NECROPSY *

By P. A. GRAY, M.D., F.A.C.P., *Santa Barbara, California*

THE clinical features of hemochromatosis as described in Sheldon's [1] excellent monograph include (1) a predominant occurrence between 35 and 60 years of age, (2) a predilection for the male sex, (3) a familial background, (4) a short life expectancy (18½ months), and (5) a diagnostic triad of symptoms:

pigmentation of the skin, diabetes mellitus, and cirrhosis of the liver. Butt and Wilder [2] and Lawrence [3] reported a longer survival period than this among their cases and predicted a reduction of the high mortality (50 per cent) noted by Sheldon [1] due to diabetic coma. They felt that improved treatment of the associated diabetes would improve the prognosis as regards duration of life and that death would henceforth follow the effects of the pathological changes in the liver. The present case confirms this prediction.

Few recorded cases of hemochromatosis have survived as long as the one described below. This patient lived 11 years after the diagnosis had been definitely established and about 13 years after the appearance of the first symptoms attributable to hemochromatosis. Almost all of the recorded complications of this disease eventually appeared. During life pigmentation of the skin, enlargement of the liver, and refractory diabetes mellitus were noted. Functional derangement of the liver, pancreas, heart, thyroid gland, pituitary gland, and brain appeared. At postmortem examination iron-containing pigment was found in these organs. It is believed that the fact that this patient was under continuous treatment throughout the course of his disease contributed to his unusually long survival.

CASE REPORT

H. W. F., a male, aged 68 years, had been a mining engineer and had lived much of his life in Mexico where he had repeatedly handled copper-containing ore. He had been a life-long abstainer. When 25 years old he had had typhoid fever, followed by an appendectomy and cholecystectomy and later in the same year a pulmonary hemorrhage. Except for this series of illnesses and occasional attacks of dysentery and malaria he had remained well until 55 years of age.

The first significant symptoms noted at that time were headaches, dependent edema of the ankles, fatigue, and loss of weight. It was reported that a tender liver margin could be felt through the upper abdominal scar. A grayish color of the skin of the face was noted and upon inquiry was admitted by the patient to have been present for the preceding two years. Glycosuria was also discovered and diabetic regimen instituted. Later in the same year the patient was examined at the Mayo Clinic by Drs. Plummer, Wilder, and Allen [4] who reported a depressed basal metabolism (— 18 per cent to — 25 per cent), slate-like pigmentation of the skin, and diabetes mellitus. A biopsy of the skin confirmed the clinical impression of hemochromatosis. Shortly thereafter a definite enlargement of the liver appeared.

Throughout the rest of the patient's life he remained in Santa Barbara under continuous medical observation. His diabetes required large doses of insulin for control. One after another of his organs showed signs of insufficiency. During the last year of life his mentality failed, necessitating admission to the Psychopathic Unit of the Santa Barbara General Hospital.

The skin which originally had been unusually white, changed first to a gray, slate color, then to a muddy brown. The exposed surfaces of the face, arms, and the lower legs took on late a fine coppery sheen. Many areas of senile keratosis and purpura appeared in the bronzed areas. Early in the course of his disease his hair became dry, coarse, and white. As the disease progressed his hair gradually fell out so that he was nearly bald before death.

The liver remained tremendously enlarged for 11 years. Its size fluctuated somewhat with the degree of compensation of the circulation but always reached to the level of the umbilicus in the anterior axillary line and midway between the xiphoid and umbilicus in the midline. The liver edge was always tender and palpation of the

organ produced pain and nausea. Toward the end of the patient's life his liver became quite hard and nodular, and appeared to occupy about one-half of the abdominal cavity. The spleen also varied in size but was always palpable. It was firm but not tender. No ascites occurred.

Nasal, esophageal, and rectal varices appeared early and progressively enlarged. The corona of tremendously enlarged hemorrhoids presented a difficult, mechanical problem in defecation. Large varices of the lower extremities played a rôle in dependent edema and handicapped the healing of superficial bruises.

Electrocardiographic evidence of myocardial damage was noted six years before death. Congestive heart failure followed two years later. Thereafter circulatory compensation was maintained with difficulty by the restriction of salt and fluid intake and by the continuous administration of digitalis. The blood pressure remained about 140 to 150 mm. Hg systolic, 80 to 90 mm. diastolic.

Macrocytic, hyperchromic anemia was present for the last 10 years of life and held under control by continuous liver and iron administration. Several gastric aspirations before the esophageal varices appeared showed free hydrochloric acid present.

Asthenia and apathy were marked from the onset of his illness and were not relieved by the administration of adrenal cortex extract. Elevation of the basal metabolic rate to physiological levels by the administration of thyroid extract did not effect any clinical improvement. Libido had disappeared before coming under treatment and never reappeared. At first the patient felt cold at all times, later he felt too warm. During the last months it became difficult to keep clothes on him because he complained constantly of his skin being burning hot.

During the first three years of treatment his diabetes was readily controlled; thereafter, however, it became more difficult to control, and after the mental breakdown almost impossible. His insulin requirement remained high and fluctuated widely from day to day; yet when viewed over a period of years there was remarkable constancy. At no time during the last seven years of life was he able to do with less than 100 units of insulin daily. Sample days over a period of 11 years are shown in chart 1. Regular or crystalline insulin was used throughout. Upon each of several

CHART I

Year	Age	Weight	Diet				Insulin	Blood Sugar	Urine Sugar
			C	P	F	Cal.	RI	Mg. %	Gm.
1929	57	162	217	93	107	2303	27	70	0
1931	59	159	202	70	101	1997	59	156	9.1
1933	61	160	179	71	89	1801	181	290	19.2
1935	63	161	188	87	96	1974	173	180	+
1937	65	152	217	92	108	2208	115	238	14.3
1938	66	154	160	80	157	2373	155	266	2.4
1940	68	150	298	97	125	2695	180	158	70.0

attempts to use protamine-zinc-insulin or histone-insulin areas of induration and inflammation developed about the sites of injection. The patient complained of "electric shocks" in these areas, which raised the interesting speculation whether reaction currents were set up between the metallic ash of these insulin-preparations and the iron pigment in his skin.

This patient never required the enormous doses of insulin which have occasionally been reported among cases of hemochromatosis, yet his glycosuria could never be

completely controlled even with six injections of insulin daily. Some evidence of resistance to insulin was seen in his poor response to crystalline insulin injected intravenously under basal conditions.

Although his diabetes was not strictly controlled over a period of 11 years, the patient's resistance to infection seemed to be about normal. He recovered from two different attacks of pneumonia and from many cuts and bruises with apparently normal promptness. Urinary tract infection did not occur, and his kidney function remained normal up to the end of his life.

The capacity of this patient to react to intravenously injected insulin was tested and compared with that of a group of diabetic and non-diabetic subjects. The method used was a modification of that described previously by Gray and Burtness.[5] In all tests in this series either two or four units of crystalline insulin were injected intravenously under basal conditions regardless of the weight or age of the subject. Capillary blood sugar specimens were collected before the injection of the insulin and at 30 and 60 minutes thereafter. All specimens were analyzed by the Malmros[6] modification of the Folin-Wu technic. Results have been expressed in the milligram per cent fall of the blood sugar below the initial level per unit of insulin injected. Experience has shown that there is no significant difference in the insulin depression curves of normal subjects dependent upon the amount of insulin injected as long as the dose is kept below five units and that the *maximum depression usually occurs in the 30 minute specimen.* No significant difference was noted between the results obtained in this patient and those from a group of non-diabetic subjects (chart 2).

CHART II

	Number of Cases	Depression of Blood Sugar (mg. %/unit)
Subject..............................		5.7± 2.0
Diabetic.............................	28	11.6±11.4
Non-diabetic.........................	51	6.9± 3.5

There was a slight difference between the patient and a group of diabetic subjects. The latter showed a somewhat greater capacity to react to intravenously administered insulin, as measured by this test, than this patient with hemochromatosis. When six times as much insulin was given to the patient as was ordinarily used for the tests done on the diabetic subjects (12 units instead of 2) an insulin depression curve was obtained which was identical with those obtained in the diabetic group when the smaller dose had been used. Hence, it was felt that some evidence of "insulin resistance" was obtained, but the degree thereof was much less than had been expected.

Necropsy Report (by Clark E. Brown, M.D.). The external examination showed the body to be that of an old white man 6 feet 1 inch tall, weighing approximately 160 pounds. The skin in general was dry and wrinkled. The head was covered with thin gray hair. The legs below the knees had a brownish color, resembling a coat of tan. The hands below the wrists were also brownish with scattered reddish-purple blotches.

The heart: all chambers appeared dilated and the ventricular musculature was flabby and brown. It had the usual thickness. The endocardium was smooth, and the valves were conspicuously delicate. The coronary arteries were soft and patent, and no atheromata were noted on multiple sections through them although roentgenogram of the postmortem specimen brought out scattered, minute calcium foci along the distribution of both branches. The arch and thoracic portions of the aorta were

smooth. The intima of the abdominal aorta contained numerous, partially calcified plaques.

The liver weighed 3910 grams. Its surface was irregularly nodular. There was a distinctly coppery color to the liver, this being more evident on the cross-section. Cut section showed the liver parenchyma separated into irregular sections by dense fibrous septi. Over the gall-bladder site were a series of yellowish white nodules, measuring up to 2 cm. in diameter. In places, hemorrhage had occurred into the nodules. In the center of this series of nodules, opaque white infiltrative hard tissue extended out into the parenchyma, giving highly suggestive evidence of an infiltrative malignant change.

The pancreas weighed 75 grams and was definitely atrophied and brownish. In the head of the pancreas there was a series of distinct opaque white nodules, the largest of which measured one centimeter in diameter (figure 1).

FIG. 1. Cut section of the liver and pancreas showing carcinomatous nodules. Pigment stain visible on liver surface beneath ruler.

The spleen weighed 690 grams, and had a distinct brownish hue. The kidneys weighed 230 grams each. The capsule was thin and stripped with ease. The cortex and medulla were dark and of good thickness. The adrenals weighed 21 grams. The thyroid weighed 27 grams. There were a few small cysts in one lobe. Otherwise, the parenchyma was firm and brown, and a moderate amount of colloid material was expressed from the cut surface on pressure. The parathyroids were small.

In the microscopic examination, all sections of the liver showed the lobular pattern destroyed by fine and dense bands of connective tissue. The latter contained

numerous distorted bile ducts, some of which appeared to be increased in size. Most of the liver cells contained brownish green granules of hemosiderin in their cytoplasm. Some of them were filled with small vacuoles and others were almost replaced by large vacuoles. These presumably contained fat. In one section, the irregularly divided clusters of liver cells merged with pleomorphic cells which had large hyperchromatic nuclei and rather scanty cytoplasm. A few contained hemosiderin but no bile. The Kupffer cells contained pigment, but the largest proportion of pigment was in the liver cells. The tumor cells in the liver resembled those in a lymph node situated near the head of the pancreas. The tumor cells were obviously of liver cell origin. Many of the liver cells showed various degrees of degeneration and necrosis. In parts of the tumor, zones of massive necrosis were present.

In the pancreas there was an extensive and generalized deposition of hemosiderin in the acinar tissue. The pancreatic lobules were scattered in abundant fatty tissue as though atrophy had occurred. The cells in some lobules were degenerated and there appeared to be a resultant fibrosis, both intralobular and perilobular. Islet tissue was singularly scarce. In the only two islets identified, masses of hyaline pressed against remaining islet cells with resultant atrophy. The islet cells contained hemosiderin granules. In the lymphatics in sections removed from the head of the pancreas, hepatoma cells could be seen. Hemosiderin granules were seen microscopically in the myocardium, the splenic capsule, the renal tubular epithelium, the granulosa layer of the adrenal cortex, the thyroid acini, the parathyroid cells and the skin. In the basal ganglion cells and the pars intermedia of the pituitary, pigment deposition was also seen. Some of this latter pigment resembled hemosiderin.

The anatomical diagnosis was hemochromatosis; cirrhosis of the liver with primary carcinoma, metastatic to the head of the pancreas; atrophy of the pancreas; fibrosis of the spleen and lymph nodes; myocardial degeneration; pulmonary edema; solitary cyst of the kidney; melanosis coli; gastric dilatation; and bronchopneumonia.

SUMMARY

A case of hemochromatosis is reported in which the patient lived for at least 11 years after the diagnosis had been established by skin biopsy. All of the usual complications appeared, including insulin-refractory diabetes. Death occurred from liver damage due to pigment deposition and malignant change. Necropsy findings are reported.

BIBLIOGRAPHY

1. SHELDON, J. H.: Hemochromatosis, 1935, Oxford University Press, New York City.
2. BUTT, H. R., and WILDER, R. M.: Hemochromatosis, Arch. Path., 1938, xxvi, 262–273.
3. LAWRENCE, R. D.: The prognosis of hemochromatosis, Lancet, 1936, ii, 1055–1056.
4. PLUMMER, W. A., WILDER, R. M., and ALLEN, E.: Personal communication.
5. GRAY, P. A., and BURTNESS, H. I.: Hypoglycemic headache, Endocrinology, 1935, xix, 549–560.
6. FOLIN, O., and MALMROS, H.: Improved form of Folin's micro method for blood sugar determinations, Jr. Biol. Chem., 1929, lxxxiii, 115–120.

COMBINED HYPERTHYROIDISM AND ADRENAL CORTICAL INSUFFICIENCY: EFFECT OF IODINE THERAPY: A CASE REPORT [*]

By Leo Gitman, M.D., Morris Ant, M.D., and Mendel Jacobi, M.D., F.A.C.P., *Brooklyn, New York*

The coexistence of hyperthyroidism and adrenal cortical insufficiency is unusual, relatively few cases having been cited in the literature. Rolleston [1] cites several early reports of skin pigmentation in advanced Graves' disease. More recent cases have been reported, chiefly by French investigators.[2, 3, 4, 5] All these cases have been adjudged, as to the adrenal component, entirely on clinical evidences alone, and only one case of Brenner's (case 4) [6] was supported by anatomical evidence. Anderson and Lyall [7] described the appearance of Addison's disease in a patient with hyperthyroidism several years after roentgen treatment of the thyrotoxic state. The diagnosis in this instance was supported by the determination of chlorides in the blood and urine. The recent contribution of Ramos and Colombo [8] has not been available to us.

This case is reported first because of the comparative rarity of the combined states and second because of the improvement in the clinical state and changes in the blood electrolyte pattern relative to the adrenal cortical insufficiency resulting from treatment of the hyperthyroid state alone.

CASE REPORT

On March 19, 1941, B. W., a white male aged 64, was admitted to the Beth-El Hospital complaining of urinary retention and hematuria. Three years prior to admission he had noted blood in his urine. He was told at that time that he had "stones in the bladder." Subsequently, he had polyuria, dysuria, and nocturia. For one month prior to admission severe dysuria was experienced. One week previously "clots" were noted in the urine. Four days previously the patient developed complete urinary retention accompanied by severe lower abdominal pain, and he was catheterized daily. He lost 37 pounds during the six months prior to admission; anorexia and constipation were prominent symptoms during this period.

From February 1924 until June 1925, he had been a patient at the Montefiore Hospital, treated there for chronic pulmonary tuberculosis, I A, with "fibrosis of both upper lobes, left more than right. Sputum from the time of his admission until his discharge was persistently negative. Blood pressure was 130 mm. Hg systolic and 90 mm. diastolic. There is no record of any disease of the thyroid or adrenal gland." [9]

Between 1928 and 1939 he had been intermittently treated in the out-patient department of the Jewish Hospital of Brooklyn for dysuria, hematuria, dyspnea on rest and exertion, and exertional precordial pain. Physical examinations, cystoscopy, and roentgenographic examinations of the chest and urinary tract were negative. Electrocardiograms (repeated) were normal except for low voltage. Blood pressures varied between 130 mm. Hg systolic and 80 mm. diastolic and 130 mm. systolic and 100 mm. diastolic. He was there considered to be suffering from asthmatic bronchitis, coronary sclerosis, and angina pectoris, with a cardiac classification of II B.

On admission, the patient was emaciated, anemic, complained of lower abdominal pain and appeared acutely ill. The tongue was dry and coated. The thyroid gland

was not palpable. The heart was enlarged to slightly beyond the midclavicular line; a rough systolic murmur was localized at the apex. The lungs were clear. The abdomen was soft; the bladder was distended. The prostate was hard, adenomatous and tender. Murphy sign was positive bilaterally. Temperature was 101° F., pulse 96, respirations 28. Blood pressure was 122 mm. Hg systolic and 78 mm. diastolic. Urine showed a specific gravity of 1.009–1.030, was alkaline, had albumin 2 plus, and many white blood cells, nowhere clumped. Blood count was 4.1 million erythrocytes, hemoglobin (Sahli) 75 per cent, leukocytes 18,100. Blood sugar was 97 mg. per cent, urea 13.3 mg. per cent. Kline (blood) negative, diagnostic and exclusion.

A two stage prostatectomy was performed. The pathologic lesions reported were: "(1) fibro-adenomatous hypertrophy of the prostate, (2) chronic prostatitis with multiple miliary abscesses, non-specific."

After the second stage operation, the patient complained of increased weakness. He was unable to void spontaneously. Seventeen days after this operation, the medical department was called in consultation.

The patient now appeared weak and apathetic, complained of pain in both thighs, and could move only with great difficulty. The outstretched fingers showed a fine tremor. There was no cough. The tongue was still dry and coated. The jaws were edentulous except for two decayed roots. The buccal mucosa showed several dark gray patches on each side, some circumscribed, others diffuse. There was a generalized dark pigmentation of the skin, more marked in the creases of the palm. The perianal region was almost black. No pretibial edema was present. The palpebral fissures were somewhat widened and a congenital left lateral strabismus was present. The thyroid gland was not palpable. The chest was flat, with depressed supra- and infraclavicular fossae. There was dullness and diminished breath sounds over the entire lung bed, with crackling medium-sized râles and bronchovesicular breathing in both infra- and supraclavicular spaces. Heart sounds were distant but not otherwise altered.

Temperature was 99.6° F., pulse 78, respirations 20. Blood pressure was now 94 mm. Hg systolic and 72 mm. diastolic. Weight 101½ pounds. The urine showed no abnormalities; albumin was no longer present and there was only an occasional white cell. Blood showed a mild secondary anemia. Blood serum sodium was 104 meq./liter,[10] serum potassium 22 meq./liter,[11] cholesterol 228 mg. per cent,[12] chlorides 104 meq./liter,[13] urea 17.8 mg. per cent, sugar 136 mg. per cent. Venous pressure was 14 cm. water; with pressure over the liver, 14.5 cm. Sputum treated with antiformin showed no tubercle bacilli (six examinations). Roentgenogram of the chest showed "the heart to be of normal size and contour. The hila are the seat of lymphatic thickening and the root branches are accentuated. Excepting for a tendency to fibrosis of the linear markings, there is no evidence of recent or active parenchymal infiltration or pleural involvement." The sella turcica showed no abnormalities on roentgenographic examination. There was no evidence of a substernal thyroid gland. The basal metabolic rate was plus 71 per cent. Glucose tolerance (when the basal metabolic rate was plus 20 per cent) showed a fasting level of 62 mg. per cent; one hour, 166 mg. per cent; two hours, 176 mg. per cent; three hours, 168 mg. per cent; four hours, 146 mg. per cent.

During the first 12 days of treatment, the patient received sodium chloride and glucose, orally and parenterally, and a total of 10 c.c. of aqueous adrenal cortical extract (Wilson) and 10 mg. desoxycorticosterone acetate, the latter two because of his extreme asthenia. Thereafter throughout his stay in the hospital no therapy directed toward the adrenal gland was used. On the above regimen, the patient showed a slight but definite improvement; there was some increase in strength, and spontaneous voiding occurred on the second day after therapy was instituted. For the next eight days he received 15 minims of Lugol's solution daily. This was discontinued for 10 days to observe the effects of its withdrawal, and then reinstituted

at a dose of 5 minims daily. The changes in the laboratory data are illustrated graphically in figures 1 and 2 and summarized in table 1.

Under treatment with Lugol's solution the electrolytic pattern of the blood, and the basal metabolic rate showed prompt improvement. The patient's symptomatic response was just as definite but not so rapid. On discharge, the patient had regained the greater part of his strength, walked easily without pain, had a very good appetite, and had reached 114 pounds in weight. His blood pressure had risen to 102 mm. Hg systolic and 64 mm. diastolic.

During the first iodine withdrawal period, there was a stationary phase in the basal metabolic rate and cholesterol values. The serum sodium fell and the potassium rose; the chloride level was roughly parallel to that of the sodium. With continued administration of iodine, these values resumed their progress toward normal levels. The second withdrawal period showed only a change in the metabolic rate.

DISCUSSION

The coexistence of hyperthyroidism and adrenal cortical insufficiency appears to be established by the data presented. The history of pulmonary tuberculosis, the profound asthenia coming on as it did after a surgical procedure of major proportion, the loss of weight, hypotension, dehydration, pigmentation, and the low serum sodium and high normal potassium levels tend to support the diagnosis. It is to be noted that the patient's most marked clinical improvement occurred during the period of administration of the Lugol's solution without specific therapy involving the use of sodium salts or adrenal gland preparations, even though the most marked blood pressure changes occurred during the period of the latter type of therapy (figure 2). It is further to be noted (figure 1) that the basal metabolic rate was not altered during the adrenal extract phase of therapy but was clearly lowered upon administration of iodine and rose upon its withdrawal; that, though the sodium level rose and the potassium fell slightly with the use of adrenal extract and sodium, these effects were much more pronounced during the period of iodine administration and were altered inversely when this was withdrawn.

The basal metabolic rate may be subnormal, normal, or elevated in Addison's disease.[14, 15] The exceedingly high rate in this case, and its response, as well as that of the cholesterol, to the administration of iodine and the inverse response upon its withdrawal indicate the presence of hyperthyroidism. The presence of a fine tremor in the hands, and the widened palpebral fissures are additional features in support of this.

In our case the question arises whether the adrenal condition was a true Addison's disease causing a secondary hyperplasia of the thyroid or whether a severe primary hyperthyroidism caused a functional adrenal cortical insufficiency.

Oehme[16] reported that adrenal cortex given to guinea pigs together with the thyrotropic principle of the anterior pituitary suppressed the increase of metabolism. This was contrary to the findings of Elmer, Giedosz, and Scheps.[17] Schacter,[18] working with dogs, failed to confirm Oehme's results. Marine and Baumann[19] demonstrated that incomplete destruction of the adrenal cortex of rabbits is followed by an increased production of body heat. This increase was not produced in thyroidectomized animals.[20] These results were corroborated in cats.[21] This led Marine to postulate adrenal cortical insufficiency as an important factor in the etiology of Graves' disease.[22] This theory was tested clinically by Shapiro and Marine[23] and Shapiro[24] who reported improvement
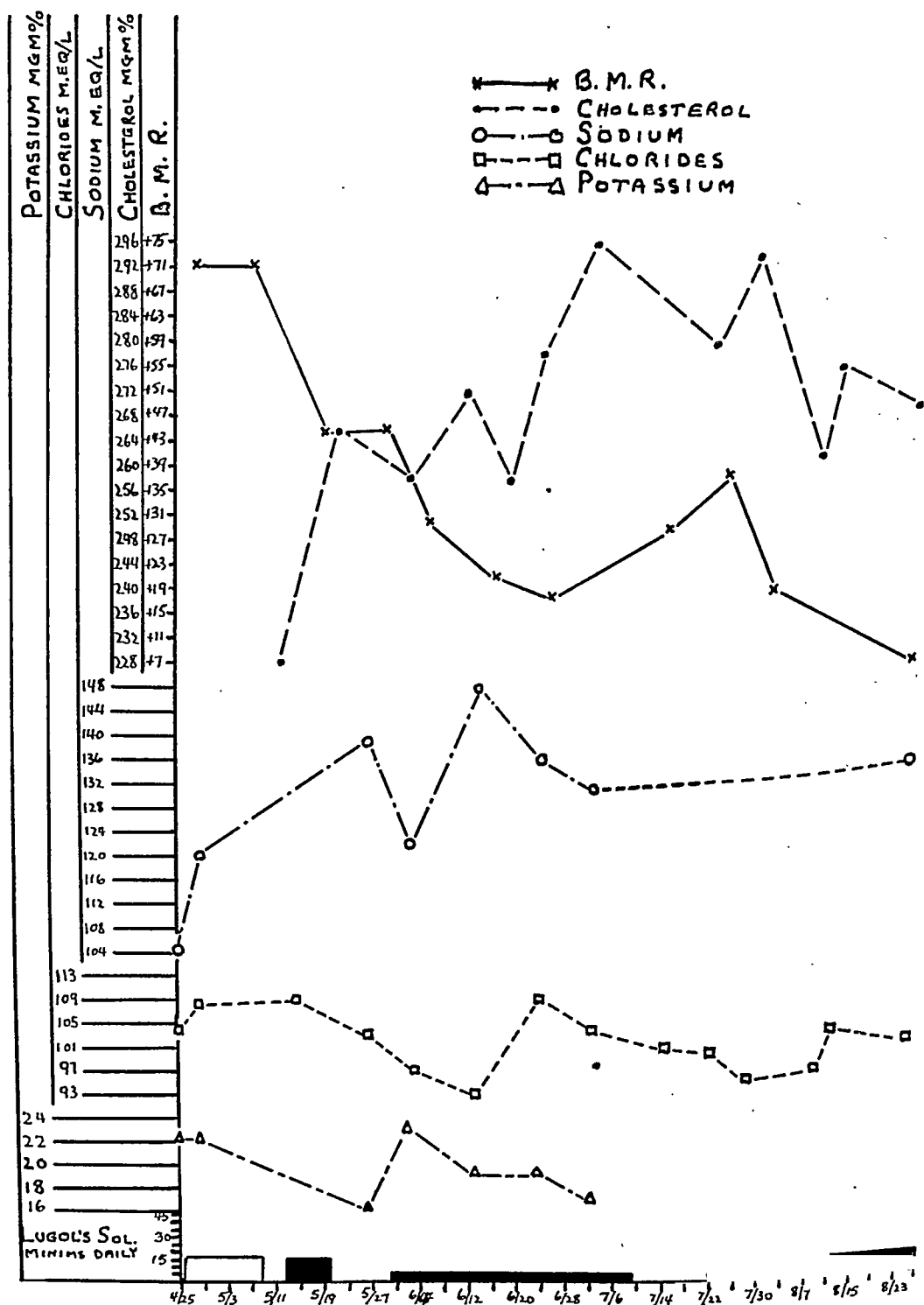
FIG. 1. Effect of Lugol's solution on blood electrolytes and cholesterol and basal metabolic rate in case of combined thyrotoxicosis and adrenal cortical insufficiency. Note that administration of Lugol's (black squares) increased cholesterol, chlorides, and sodium, and depressed potassium and basal metabolic rate, and that its withdrawal produced opposite effect. Small amounts of desoxycorticosterone (white squares) elevated sodium and slightly chlorides but produced no other changes.

of patients suffering from Graves' disease upon the administration of adrenal cortex. This work was not confirmed by the careful investigations of Wein-stein and Marlow.[25]

In the light of Marine and Baumann's work, our patient might be considered a clinical counterpart of the experimental rabbit. The possibility that the adrenal cortical insufficiency was the cause of the thyroid hyperplasia cannot be defi-
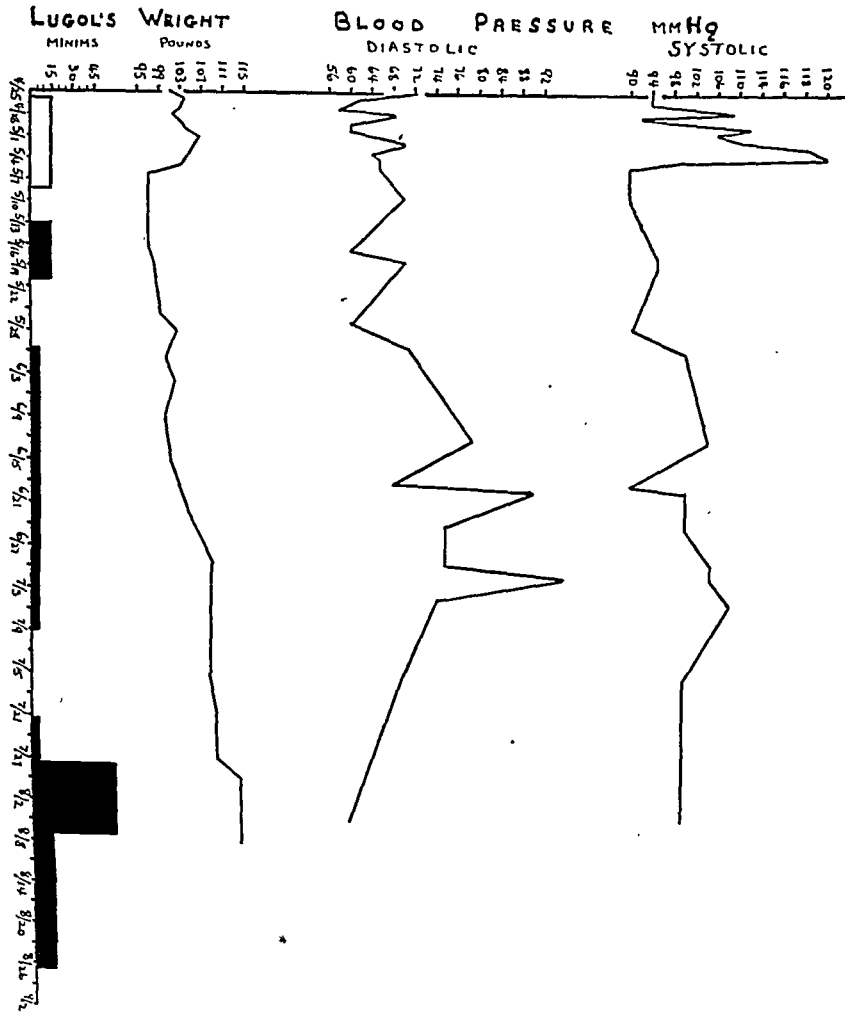
FIG. 2. Effect of Lugol's solution on blood pressure and body weight in case of combined thyrotoxicosis and adrenal cortical insufficiency. Note that, while desoxycorticosterone (white squares) caused the greatest systolic rise, this had returned to original subnormal level during its administration, as did the weight. On Lugol's solution (black squares) blood pressure rise and weight increase were more moderate but sustained.

nitely ruled out. Against this view, however, may be advanced the arguments that experimental chronic adrenal insufficiency is not characterized by an increased basal metabolic rate, the reverse, in fact, being true; the rare incidence of hyperthyroidism in Addison's disease; the response of the blood electrolytes to thyroidal therapy and their maintenance in normal pattern without specific adrenal extract therapy in the case described as noted above.

The mechanism of the maintenance of the blood electrolytes within the normal range is obscure. A possible explanation may be as follows: The adrenals, presumably damaged by a tuberculous process in this case, had a decreased "reserve," of a subclinical grade. The greatly increased metabolism, the result of the increased thyroidal activity, demanded an increased secretion from the adrenal cortex beyond its reserve, as a result of which the patient exhibited signs of insufficiency. With lowering of the metabolic rate as the result of the iodine therapy, the requirement for cortical hormone decreased to a level

TABLE I

Effect of Iodine Therapy on Laboratory Data in Case of Combined
Thyrotoxicosis and Adrenal Cortical Insufficiency

Date	Sodium meq/l	Potassium meq/l	Chloride meq/l	Sugar mg. %	Cholesterol mg. %	Urea mg. %	B.M.R.	Remarks
3/21				97		13.3		
4/21				93		14.6		
4/25	104	22	104	136		17.8		100 gm. glucose
4/28	120	22	108	96		9.4	+71	4 c.c. adrenal extract, 34 gm. saline
5/8							+71	Specific therapy discontinued
5/12					228			
5/14			109					Lugol's 15 minims daily begun
5/19							+44	
5/21					226			
5/26	139	16.1	103					Lugol's discontinued
5/29							+45	
6/2	122	23.2	97		258			Lugol's 5 minims daily begun 5/30
6/5							+30.2	
6/11					272			
6/13	148	19	93	89		12.6	+21	
6/16								
6/18					258			
6/23	136	19.6	109		278			
6/25							+18	
7/2	131	16.7	104		296			
7/14			101				+29	Lugol's discontinued on 7/9
7/21			100.5		280			
7/24							+38	Lugol's 5 minims daily begun 7/22
7/28			96		294			Lugol's 45 minims daily begun
7/31							+19	
8/8			97		262			Lugol's 15 minims daily begun
8/11			103.9		276			
8/25	135	16	101		270		+ 7	

again within the limits of the adrenal reserve, with improvement for the patient, as indicated by the clinical and laboratory data.

There is evidence in the literature to support this view. Thyroid feeding to experimental animals produced adrenal hyperplasia.[26, 27, 28] Zwemer[29] showed that thyroid feeding greatly reduced the survival rate of adrenalectomized rats. This was confirmed on cats by Carr and Conner.[30] In our own case, the definite reversal in the values of serum sodium and potassium during the first iodine withdrawal period and the decreased sugar tolerance lend support to this hypothesis.

SUMMARY

A case of combined hyperthyroidism and adrenal cortical insufficiency is described. The administration of Lugol's solution controlled the basal metabolic rate, brought the blood cholesterol and electrolytic pattern within the normal range, and produced marked improvement clinically in the symptoms of both states.

The blood electrolytes were maintained at normal levels with the use of Lugol's solution alone, and tended to revert to a subnormal pattern (low sodium, high potassium) upon withdrawal of the iodine.

The sequence of events is believed to be as follows: Hyperthyroidism caused a functional adrenal cortical insufficiency due to an increased requirement of cortical hormone and decreased "reserve," probably due to previous subclinical pathological alteration of the adrenal. Administration of iodine lowered the metabolic rate and hence the demand for cortical hormone to a level within the reserve of the gland, with consequent alleviation of the symptoms of adrenal cortical insufficiency.

BIBLIOGRAPHY

1. ROLLESTON, H. D.: The endocrine organs in health and disease, 1936, Oxford University Press, London, page 244.
2. ETIENNE, G.: Addisonisme total, syndrome polyglandulaire par dysthyroidie et dyssurrenalie, Bull. et mém. Soc. méd. d. hôp. de Paris, 1910, i, 824–829.
3. ETIENNE, G., and RICHARDS, G.: A propos d'un syndrome Basedowien d'origine émotive survenu chez un Addisonien. Etude pathogenique, Bull. et mém. Soc. méd. d. hôp. de Paris, 1918, xlii, 1199–1203.
4. CHAUFFARD, A., and GIROT, L.: Pathogenie thyro-surrenale du Basedowisme, Rev. franç. d'endocrinol., 1925; iii, 145–153.
5. ETIENNE, G., and RICHARDS, G.: Maladie de Basedow et Addisonisme, Rev. franç. d'endocrinol., 1926, iv, 1–11.
6. BRENNER, O.: Addison's disease with atrophy of the cortex of the suprarenal, Quart. Jr. Med., 1928, xxii, 121–137.
7. ANDERSON, I. A., and LYALL, A.: Addison's disease due to suprarenal atrophy with previous thyrotoxicosis and death from hypoglycemia, Lancet, 1937, i, 1039–1043.
8. RAMOS, A. G., and COLOMBO, E. O.: False hyperthyroidism due to suprarenal insufficiency, Bol. Inst. de Matern., 1939, viii, 287–292.
9. Personal communication from Dr. Leonard Reich, resident physician, Montefiore Hospital, Bedford Hills, New York.
10. BUTLER, A. M., and TUTHILL, E.: An application of the uranyl zinc acetate method for determination of sodium in biological material, Jr. Biol. Chem., 1931, xciii, 171; modified by SOBEL, A. ET AL.: Jr. Biol. Chem., 1941, cxl, 501.
11. KLEIN, B., and JACOBI, M.: The determination of small amounts of potassium, Indust. and Eng. Chem., Anal. Ed., 1940, xii, 687–689.
12. SAIFER, A., and KORNBLUM, M.: Determination of chlorides in biological fluids by the use of absorption indicators, Jr. Biol. Chem., 1935, cxii, 117–124.
13. KAYE, L. A.: Determination of total and free cholesterol in blood serum, Jr. Lab. and Clin. Med., 1940, xxv, 996–1001.
14. ROLLESTON, H. D.: reference 1, page 351.
15. GREENE, C. H.: Further studies in Addison's disease, Proc. Staff Meet. Mayo Clin., 1931, vi, 305–310.

16. OEHME, C.: Nebennierenrindenhormon, Ascorbinsaüre und Aminosaüren bei experimenteller Hyperthyreose, Arch. f. exper. Path. u. Pharmakol., 1937, clxxxiv, 558–572.

17. ELMER, A. W., GIEDOSZ, B., and SCHEPS, M.: L'action, chez le cobaye, de la cortine sur l'hyperactivité de la thyroide provoquée par la thyréostimuline préhypophysaire, Compt. rend. Soc. de biol., 1935, cxviii, 1373–1374.

18. SCHACTER, R. J.: Effects of adrenal cortical extract on experimental hyperthyroidism in dogs, Proc. Soc. Exper. Biol. and Med., 1938, xxxix, 409–410.

19. MARINE, D., and BAUMANN, E. J.: Influence of glands with internal secretion on the respiratory exchange. II. Effect of suprarenal insufficiency (by removal or freezing) in rabbits, Am. Jr. Physiol., 1921, lvii, 135–152.

20. MARINE, D., and BAUMANN, E. J.: Influence of glands with internal secretion on the respiratory exchange. III. Effect of suprarenal insufficiency (by removal) in thyroidectomized rabbits, Am. Jr. Physiol., 1922, li, 353–368.

21. DAVIS, J. E., and HASTINGS, A. B.: Relationship of the adrenal and thyroid glands to excised muscle metabolism, Am. Jr. Physiol., 1933, cv, 110–121.

22. MARINE, D.: Studies on the etiology of goiter including Graves' disease (McBride Lecture), ANN. INT. MED., 1930, iv, 423–432.

23. SHAPIRO, S., and MARINE, D.: Clinical report of a case of Graves' disease with rapid improvement following the oral administration of fresh ox suprarenal gland, Endocrinology, 1921, v, 699–707.

24. SHAPIRO, S.: Further observations on feeding interrenal gland in cases of Graves' disease, Endocrinology, 1924, vii, 666–676.

25. WEINSTEIN, A. and MARLOW, A.: The use of suprarenal cortex in the treatment of disorders of the thyroid gland, Bull. Johns Hopkins Hosp., 1933, lii, 408–420.

26. HERRING, P. T.: The adrenalin content of the suprarenals of the female white rat and changes brought about by thyroid feeding and other conditions, Quart. Jr. Exper. Physiol., 1920, xii, 115–123.

27. HOSKINS, R. G.: Thyroid activity as a factor in adrenal activity, Jr. Am. Med. Assoc., 1910, lv, 1724–1725.

28. PRESTON, M. I.: Effects of thyroxin injections on the suprarenal glands of the mouse, Endocrinology, 1928, xii, 323–334.

29. ZWEMER, R. L.: An experimental study of the adrenal cortex. II. Prolongation of life after complete epinephrectomy, Am. Jr. Physiol., 1927, lxxix, 658–665.

30. CARR, J. L., and CONNER, C. L.: Animal experiments with adrenal cortical extracts, ANN. INT. MED., 1933, vi, 1125–1230.

REPORT OF A CASE OF XANTHOMA TUBEROSUM TREATED WITH LIPOCAIC *

By B. D. ROSENAK, M.D., F.A.C.P., *Indianapolis, Indiana*

SEVERE disorders of fat metabolism are not extremely rare and the following case report is not submitted because of the rarity of the condition, but rather to relate the results of certain therapeutic efforts in this disease.

CASE REPORT

The patient was a white woman 49 years old at the time of examination in May 1939. She then complained of bright orange colored nodules on the palms of her hands, on the elbows, feet, knees and other areas of the skin which were frequently

irritated by friction. This condition was of about four years' duration and was becoming more extensive. It had been noticed soon after a series of roentgen-ray treatments for a fibroid tumor of the uterus. She had not menstruated since this therapy, but had no other symptoms suggestive of the menopause. She stated that she had similar skin lesions for a short time 27 years previously, during the latter months of pregnancy. This cleared up after delivery and there had been no recurrence until the onset of the present illness. About six months prior to this examination she had complained of constricting pains around the chest and had been diagnosed and treated for coronary artery disease with almost certain coronary occlusion. She also complained of constipation, gas and bloating. There was no history of jaundice or of right upper quadrant pain. There was no dyspnea, edema or chest pain at the time of this examination. The family history was negative for illnesses similar to that presented by this patient.

On physical examination she was found to be a well developed, somewhat undernourished woman. Physical examination of the heart and lungs was normal. The outstanding finding consisted of conglomerate but not confluent masses of bright orange pigment in the skin of the palms, elbows, heels, knees and dorsum of the feet. The lesions varied in diameter from less than a millimeter to about a centimeter. They were markedly elevated in all locations except the palms of the hands in which situation they were somewhat flatter.

FIG. 1. Xanthomatous lesions on the extremities.

The laboratory data at the time of the original examination was as follows: Urinalysis showed a faint trace of albumin. Hemoglobin was 78 per cent. Red cell count 3.96 millions. White count 5,200 with 50 per cent adult polymorphonuclear cells, 15 per cent band cells, 2 per cent eosinophiles, 1 per cent basophiles, 4 per cent metamyelocytes, 1 per cent myelocytes and 27 per cent lymphocytes. The cell volume was 38 per cent. The sedimentation rate was 35 mm. per hour. The Wassermann, Kahn and Hinton tests were negative. The fasting blood sugar was 98.5 mg. per cent. The glucose tolerance curve was: Fasting 98.5 mg.; 30 min.—161 mg.; one hour—175 mg.; two hours—119 mg.; three hours—79 mg. This test was regarded as conclusive in excluding diabetes mellitus. The Mosenthal test showed a reduced concentrating power of the kidneys.

The initial serum cholesterol was 700 mg. and the cholesterol esters 426 mg. The chart shows the variations which occurred during 30 months of observation. The normal value for serum cholesterol may vary considerably according to different authorities; however, variations between 150 and 250 are generally considered to be normal for total cholesterol of which 40 per cent to 60 per cent is in the form of esters. It has been pointed out by Thannhauser that most of the increase in the blood cholesterol level in xanthomatosis occurs as an increase in esters. The values

for esters in the present series of tests reveals a higher proportion of esters than normal.   Elevation of other blood lipids also occurs in xanthomatosis, but the increase in fatty acids and phospholipids is usually less pronounced than that of cholesterol and cholesterol esters.

The basal metabolic rate was minus 10 per cent.   A roentgenogram of the heart and aorta revealed no abnormalities.   Roentgenographic examination of the gall-bladder after oral administration of the dye showed normal visualization and no stones. An electrocardiogram showed the T-waves in Lead I to be of low voltage.   The T-waves in Lead III were inverted.   The S–T segment in Lead II was somewhat depressed.   No more definite evidences of coronary artery disease were seen at this time.
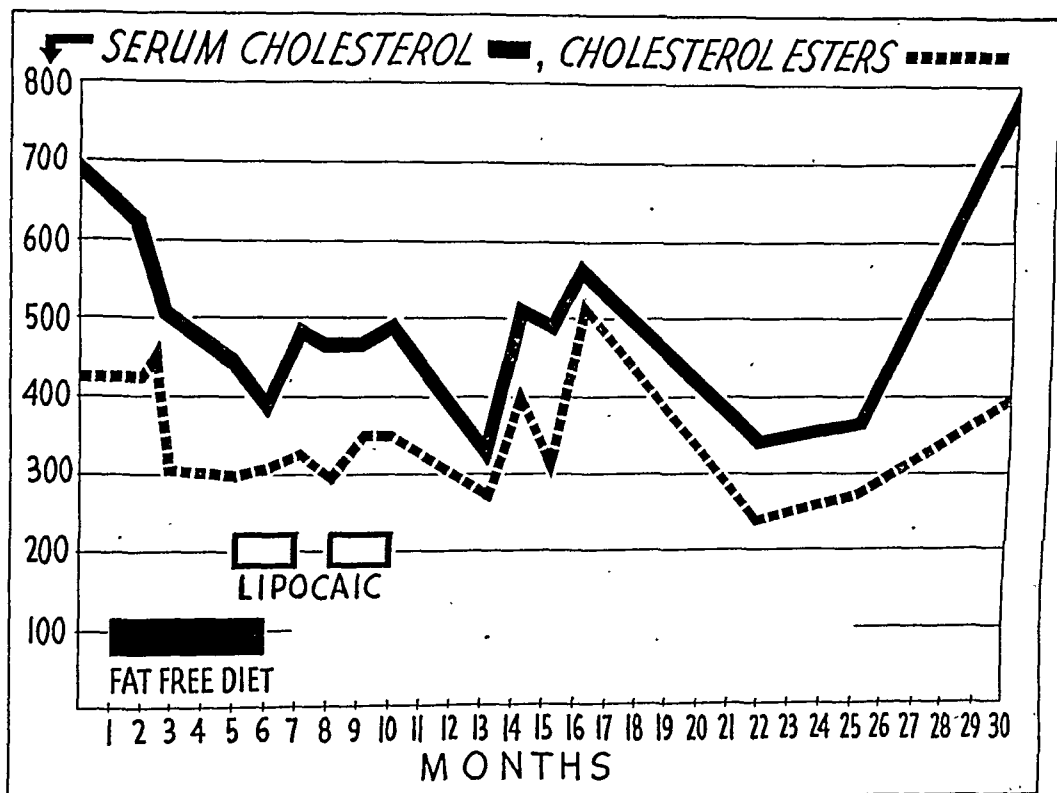
FIG. 2.   The effect of fat-free diet and lipocaic on the serum cholesterol and cholesterol esters.

This case was considered to be a typical instance of xanthoma tuberosum. According to Thannhauser [1] this condition belongs to the class of essential xanthomatoses, which he defines as "a heredofamilial constitutional disorder of the intracellular metabolism of reticuloendothelial elements and histiocytes." It is characterized by an increase in the cholesterol content of the cells.   The cholesterol concentration in the blood may be elevated or normal.   In the hypercholesteremic type the deposits tend to occur in the skin, tendons, liver, bile ducts and blood vessels.   In the normocholesteremic group the bones, brain, lungs and lymph nodes may be involved.   Schiller-Christian disease is an example of the latter type.   No histologic difference is noted in the two types. The essential abnormality is the presence in the tissues of xanthoma cells.   These are variable sized cells usually containing two nuclei and having a reticular cyto-

plasm in which there are numerous fat droplets. This fatty substance is cholesterol and cholesterol ester. The etiology of these diseases is obscure. It is the belief of Thannhauser that there is some disorder of the intracellular metabolism in the embryonal reticular cells. There are many evidences against the theory that there is a general disturbance of cholesterol metabolism; for example, the disease may occur with normal or elevated blood cholesterol and in cases treated by diet with subsequent reduction of the blood cholesterol there is. no associated disappearance of the skin lesions.

The present case demonstrates the last point. The patient was placed on a low fat, low cholesterol diet. This consisted in the elimination of all animal fats such as eggs, butter, cream, and fat meats. The prompt effect of this management on the blood concentration of cholesterol is shown by the chart. No improvement in the condition of the skin was observed.

An attempt to alter further the concentration of blood fats and possibly of the cutaneous deposits was made by the oral administration of lipocaic. This drug was described by Dragstedt [2] as a pancreatic hormone which prevented the deposition of fat in the liver of depancreatized dogs. It is thought to be a hormone which plays some part in the transport and utilization of fats. Some clinical evidence of its efficiency in reducing the fat concentration in the liver in diabetes has been described. It has also been used in other disorders of fat matabolism with results that are not very convincing. The patient received 30 grains daily for two months. During this time no change was observed in the skin lesions. The serum cholesterol fell from 454 mg. to 400 mg. during the first month of this period. During the second month on lipocaic the patient was advised to return to her normal diet. This resulted in a sharp rise in the cholesterol to 493 mg. in spite of continuing the lipocaic. The strict diet was then resumed and the drug was stopped and for the next month no significant change took place. Then lipocaic was started again in doses of 45 grains daily and this was continued for the next two months with no apparent effect on the skin condition and with very little change in the cholesterol. For the next 15 months the patient was kept on the fat free diet alone except for a brief period of administration of estrogenic hormone which the patient stopped against advice. The influence of the glands of internal secretion on lipoid metabolism is not well understood. It is not considered very likely that the artificially induced menopause had anything to do with the onset of the xanthomatosis, yet a trial of estrogenic therapy was considered worth while. The patient received four injections of 10,000 international units at weekly intervals with no improvement in the skin lesions or appreciable alteration of the cholesterol concentration in the blood. The fluctuations in blood cholesterol during this period were undoubtedly due to variations in adherence to the diet. From the twenty-fifth month to the thirtieth month she did not adhere to the diet and the last serum cholesterol was 800 mg. The skin lesions gradually became more extensive and larger. No evidence of regression of the lesions was ever noted.

Another therapeutic attempt was made to influence the cutaneous lesions. Having observed apparent regression of xanthoma deposits in the bones in Schiller-Christian disease following roentgen-ray therapy it was decided to try irradiation in this case. The hands were, therefore, treated on the palmar surfaces. The dose used was 700 r of lightly filtered roentgen-ray to each hand

given in two treatments. No evidence of improvement of the skin lesions was seen following this therapy.

Comfort and Shepard[3] of the Mayo clinic report their experience with the use of lipocaic in a case of xanthomatosis with biliary cirrhosis in which hyperlipemia, skin lesions, hepato- and splenomegaly coexisted. They observed no benefits from fat free diet alone or from diet plus lipocaic.

It is concluded from this case that it is possible to lower the serum cholesterol in xanthomatosis tuberosum by exclusion of animal fats from the diet, but that this reduction of blood fats is not accompanied by improvement of the skin lesions. Lipocaic in the doses administered to this patient had no effect on either the concentration of the serum cholesterol or on the skin lesions. Roentgen-ray therapy had no apparent effect on the cutaneous deposits.

BIBLIOGRAPHY

1. THANNHAUSER, S. J.: Lipidoses: disease of the cellular lipid metabolism, Oxford Medicine, 1940, Oxford Univ. Press, New York, Vol. IV, part I, page 214.
2. DRAGSTEDT, L. R.: Lipocaic, Northwest Med., 1938, xxxvii, 33–36.
3. COMFORT, M. W., and SHEPARD, V. D.: Xanthomatous biliary cirrhosis: report of a case, Proc. Staff Meet. Mayo Clin., 1941, xvi, 374–377.

LEUKOERYTHROBLASTIC ANEMIA WITH DIFFUSE OSTEOSCLEROSIS *

By JOSEPH MENDELOFF, M.D., and JULIUS ROSENTHAL, M.D.,
New York, N. Y.

THIS report is that of a case of a severe progressive anemia with osteosclerosis. The clinical picture as well as the pathological findings we deem to be of sufficient interest for detailed description.

CASE REPORT

The patient, a male, white, born in the U. S., a clerk by occupation, was admitted to the Welfare Hospital for Chronic Diseases on November 11, 1939, with chief complaint of anemia of seven years' duration, weakness, dyspnea on exertion, and swelling of legs and scrotum.

History before admission to Welfare Hospital: In July, 1934, at the age of 52, he was advised to have 10 teeth removed; the reason is unknown. Shortly thereafter he began to complain of dyspnea on exertion and night sweats. He was also found to be anemic by a family physician.

Between July 1934 and November 1939, the following information appeared in the case history: In January, 1935, splenomegaly was discovered for which splenectomy was performed. The spleen weighed eight pounds and had multiple infarcts. Impression: "Possible Hodgkins." In October 1935, the patient complained of dyspnea, weakness, and tingling of lower extremities. Roentgenograms of the skull and right femur were negative. In April 1936, roentgenograms of femurs showed no abnor-

malities. In October 1937, roentgenogram of the skull was negative. In February 1938, roentgenograms of the right shoulder, left hip, and skull were negative. Blood pressure was 210 mm. Hg systolic and 160 mm. diastolic. In June 1938, ascites was present. Blood pressure was 155 mm. Hg systolic and 55 mm. diastolic. In June 1939, an enlarged liver and bilateral papilledema were observed. Roentgenogram of the spine showed hypertrophic osteoarthritis. In July 1939, there was a severe hemorrhage following removal of a loose tooth. In October there was a hemorrhage from the gums; the epitrochlear lymph nodes were palpable.

For laboratory findings prior to admission to Welfare Hospital, see tables 1 and 2.

Family history: Mother died at the age of 54 of carcinoma, type unknown. Father died at the age of 70 years of heart disease. The patient had been married 30 years; there were no children.

Examination on admission to Welfare Hospital: Temperature 100.2° F., pulse 88, respiration 22. Blood pressure was 165 mm. Hg and 75 mm. diastolic. Conjunctivae were pale. The mouth and throat showed no abnormalities. The lungs were clear and resonant. Heart, apex at sixth intercostal space between mid-clavicular and anterior axillary lines. There was a soft systolic murmur at the apex. The pulmonic second sound was louder than the aortic second. Regular sinus rhythm. There was a mass in the upper abdomen, apparently liver, with lower edge palpable four fingers below costal margin. A longitudinal scar was present on the left upper quadrant of the abdomen. A few small epitrochlear glands were present. The skin was gray and dry.

Blood picture: see table 3.

Laboratory findings: See table 4.

Résumé of roentgenographic findings (reported by Dr. Henry K. Taylor): The skull, spine, ribs, pelvis, and practically all the long bones showed a generalized increase in density with no morphological alterations in structure or contour.

Course in hospital: The patient frequently presented dyspnea and orthopnea while at rest. There was marked edema of both lower extremities reaching to the level of the middle of the back. He showed slight fever. On February 24, 1940 he had two severe attacks of dyspnea accompanied by a change of his cardiac rhythm to fibrillation. He developed generalized anasarca and died March 6, 1940.

Autopsy: The autopsy was performed 16 hours after death.

External examination: Marked generalized anasarca, skin pale and slate blue in color. No petechiae or hemorrhages present.

Chest: Bilateral pleural effusions, left 750 c.c., right 850 c.c.; fluid was turbid with a greenish tint, contained fibrin flakes. Specific gravity was 1.012, cell count 500 per cu. mm. There was marked edema of both lungs, and congestion of both lower lobes.

Heart: Pericardial cavity contained 320 c.c. of turbid greenish fluid containing fibrin. Specific gravity was 1.013, cell count 600 per cu. mm. The heart was globular, enlarged to right and left, weight 650 grams, flabby. Left ventricle was 18 mm. thick, right ventricle 7 mm. The myocardium was pale. The mitral leaflets were slightly thickened. Small friable vegetations were present on the line of closure. There was slight hypertrophy of the papillary muscles of the left ventricle. The pulmonic and tricuspid valves were normal. On the ventricular surface of aortic leaflets, small vegetations, 1 to 5 mm. in diameter, friable and white gray in color, were present. Cusps were normal. Coronary arteries were patent, and showed a few atheromatous plaques. Aorta showed slight atheromata.

Abdomen: The omentum was adherent to the anterior abdominal wall at the site of the postoperative scar. 2200 c.c. of greenish turbid fluid were removed. Specific gravity was 1.014, cell count 600 per cu. mm.

The liver weighed 3900 grams. There were fibrin deposits on the surface. On

TABLE I

Blood Picture (Before Admission to Welfare Hospital)

Date	Hgb.	R.B.C.	W.B.C.	Myelo-blasts	Myelo-cytes	Meta-myelo-cytes	Mature			Lymph.	Mono.	Miscellaneous	Remarks
							N	E	B				
Jan. 1935	86%	4,350,000											Following splenectomy
Nov. 1935	78%	4,150,000	44,810										Following transfusion
Apr. 1936	25%												
Apr. 1936	54%												Following transfusion
Jan. 1937	30%												
Jan. 1937	57%												Following transfusion
Aug. 1937	44%	2,930,000											
Aug. 1937	69%	4,200,000											
Oct. 1937													Diagnosis "erythro-blastic anemia"
June 1938	37%	2,300,000	80,000		37		11			5		Normoblasts 43 Unclassified 4	
July, 1939	55%	2,650,000											Following transfusion
July, 1939	42.7	2,430,000	9,100			32	43	2		19	4	Reticulocytes 1.3 Normoblasts 101 per 100 w.b.c. Corrected ESR 18 M.C.V. 90 cu/m Bleeding time 1½ min. Coag. 8 min.	
Aug. 1939	40%	1,850,000											Following hemorrhage due to removal of loose tooth
Oct. 1939			13,300			18.5	45	0	.5	30.5	1	Reider 0.5 Unclassified 35 Aniso., poikilo., baso-philic stippling 17.5, normoblasts per 100 w.b.c.	

TABLE I—*Continued*

Date	Hgb.	R.B.C.	W.B.C.	Myelo-blasts	Myelo-cytes	Meta-myelo-cytes	Mature			Lymph.	Mono.	Miscellaneous	Remarks
							N	E	B				
Oct. 1939 attempted sternal puncture				1 pro-myelo-cyte	2	22	22	0	0	44	3	Reider 2 Unclassified 4 24 normoblasts per 100 w.b.c.	Resembles peripheral blood
Oct. 1939		670,000	6,430	2 pro.	2	15	32	0	2	40	4	Platelets 1,110,000? Plasma cell 1% 52 normoblasts per 100 w.b.c.	

TABLE II

Laboratory Data (Before Admission to Welfare Hospital)

Date	Blood Chemistry							Urine				Microscopic and Other	Other Tests
	Glu.	N.P.N.	Urea N	Total Prot.	Alb.	Glob.	Miscellaneous	S.G.	React.	Alb.	Glu.		
June, 1939	167	34	17				Van den Bergh immediate direct negative, delayed direct positive. Serum bilirubin 1.3					Trace of bile, no urobilinogen	Spinal and blood Wassermann negative. Colloidal gold negative. Creatinine 1.3

TABLE III

Blood Picture at Welfare Hospital

Date	Hgb.	R.B.C.	W.B.C.	Myelo-blasts	Myelo-cytes	Meta-myelo-cytes	Mature			Lymph.	Mono.	Miscellaneous	Remarks
							N	E	B				
Nov. 16, 1939	31%	1,940,000	8,200	1 pro. 1	2	19	37	3	0	34	3	Volume index .94 Platelets 250,000 Retic. 1.4 Normoblasts 11 per 100 w.b.c. Anisocytosis Microcytosis Sed. rate 11.5 Wintrobe	Leukoerythroblastic anemia
Nov. 21, 1939												Clot retraction 2 hours	
Nov. 24, 1939	40%	1,680,000	10,250			23	48			29		Normoblasts 15 per 100 w.b.c. Achromia, aniso, poik., etc.	Fragility .55–.20 Bleeding time 3 min. Clotting time 6 min.
Dec. 1, 1939	42%	2,140,000	8,250			14	52			34		Color index 1.0 Prothrombin 10 min. Platelets 225,000 Retic. 1% Normoblasts 13 per 100 w.b.c.	
Jan. 10, 1940	35%	1,800,000	10,250	pro. 1	12	13	52	2		13	1	Normoblasts 2 per 100 w.b.c.	After transfusion
Jan. 27, 1940	22%	2,030,000	6,450	pro. 4	1	14	58			23		Normoblasts 5 per 100 w.b.c.	
Feb. 6, 1940	28%	1,240,000	5,600	pro. 1		10	58			30	1		
Mar. 1, 1940	21%	1,370,000	8,000			18	65			46	1	Color index .8 Platelets 110,000	

TABLE IV

Laboratory Data at Welfare Hospital

Date	Blood Chemistry							Urine					Other Tests
	Glu.	N.P.N.	Urea N	Total Prot.	Alb.	Glob.	Miscellaneous	S.G.	React.	Alb.	Glu.	Microscopic and Other	
Nov. 14, 1939								1010	acid	2+	neg.	Negative	Wassermann and Kline negative
Nov. 16, 1939		32.8	13.5										Stool-Benzidine positive
Nov. 17, 1939													
Nov. 20, 1939							Uric acid 4.4 Cholesterol 329.9						Icteric index 5. Wassermann and Kline negative. Van den Bergh negative direct
Nov. 21, 1939												Bile negative	
Nov. 27, 1939													Urine concentration: 5 a.m. 220–1010 7 a.m. 215–1009
Nov. 29, 1939				7.14	4.46	2.68	Cholesterol 265.5						
Dec. 5, 1939							Cholesterol 268.0 Cholesterol esters 182.5 mg.						
Jan. 8, 1940	116		10.5				Phosphatase 7.29 B.U.						
Jan. 15, 1940				5.95	4.26	1.69	Ca. 8.6 Ph. 3.9						

section it was yellow-brown.   Many pale yellow specks, 1.5 mm. in diameter, were noted, as well as many small petechial hemorrhages.   Portal circulation was normal. Intrinsic and extrinsic biliary system was normal.

Gall-bladder was normal.

The pancreas weighed 150 grams.   It was firm and lobulated.

Genitourinary tract: The left kidney weighed 170 grams, the right kidney 300. The capsule stripped easily.   There were a few sparse, flat, irregular, depressed scars on surface.   The cortex and medulla were sharply demarcated.   Both pelves were slightly dilated.   Both ureters were patent, and the right was dilated.

Bladder, prostate, adrenals, and thyroid were normal.

The parathyroids were not found.

Lymph nodes: Cervical, peritracheal, peripancreatic, aortic and retroperitoneal nodes were found to be enlarged.   Some were discrete, others matted.   Most were pale white and of rubbery consistency.   Some were reddish brown.
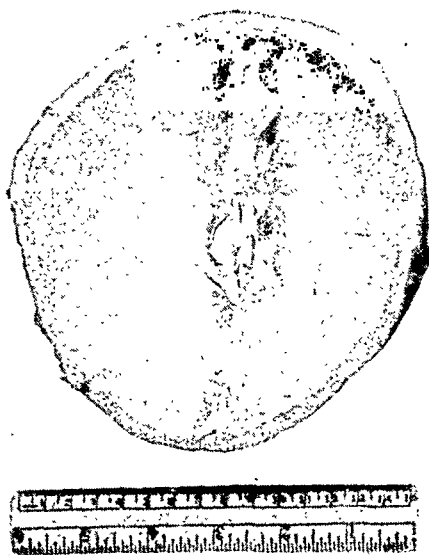
FIG. 1.   Illustrating thickness and sclerosis of calvarium.

Skeletal: Calvarium (figure 1) was 1 cm. thick.   The cortical bone was homogeneous, the marrow space absent and the quantity of red marrow slight.   Ribs and sternum showed increased thickness, were dense and hard throughout.   Marrow cavity was diminished in size; the marrow was red and scant.   The vertebrae showed marked bony sclerosis, were hard and dense; the marrow was scant.   In the left femur (figure 2) only a thin marrow channel was present in the middle third.   It contained a small amount of reddish yellow gelatinous marrow in the midst of bony trabeculation. The diameter of this cavity was 1 cm.   The remainder of bone, including both ends, was dense and sclerotic with dense rim of bone on surface.

Histological:

The spleen (figure 3) had been removed in 1935.   A review of the slide showed the capsule to be thickened.   The architecture of the spleen was distorted by an increased cellularity and apparent thickening of the cords of Billroth.   The lymph

follicles were diminished in size and quantity. A few small hemorrhagic foci were seen. There was hemosiderosis in areas. The outstanding feature of the section was the presence of many multinucleated giant cells. These were of more than one variety. They varied in size from 15.0 to 32.2 mu. Their shape was irregular; the cytoplasm was eosinophilic; some contained hemosiderin. The nuclei were vesicular, polymorphous and monstrous in shape. They were arranged in heaped up clusters in the
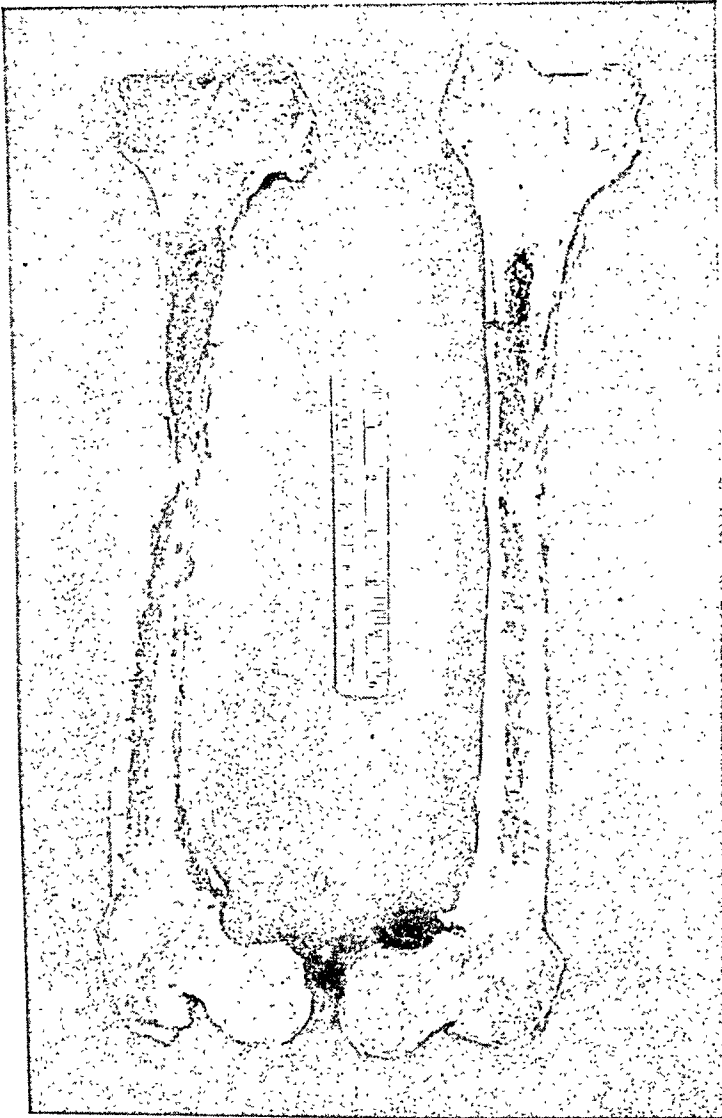
FIG. 2. Illustrating sclerosis of femur and diminution of marrow cavity.

centers of some cells, and peripherally in others. The remainder of the cells comprising the parenchyma consisted largely of myeloid cells with some reticulum cells and lymphocyte-like cells. There were also a few small islets of erythropoiesis seen.

Skin biopsy: Stain for iron negative.

Adrenal: The loose periadrenal fat tissue contained many cells of myeloid and lymphoid type. There were also plasma cells, histiocytes and monster giant cells re-

sembling those seen in the spleen except that they were smaller and their nuclei had a tendency to be hyperchromatic.

Skeletal: Skull: Marked thickening and an increase in the number of bony trabeculae were found. Marrow spaces were small and contained scant loose and matted elongated marrow cells and fibroblasts. Hematopoietic cells were scant; some lymphocyte-like cells were present. Rib: distinction between cortex and medullary space was lost. Both layers were similar and contained many irregular thickened bony trabeculae. The marrow spaces were small and distorted. Their contents
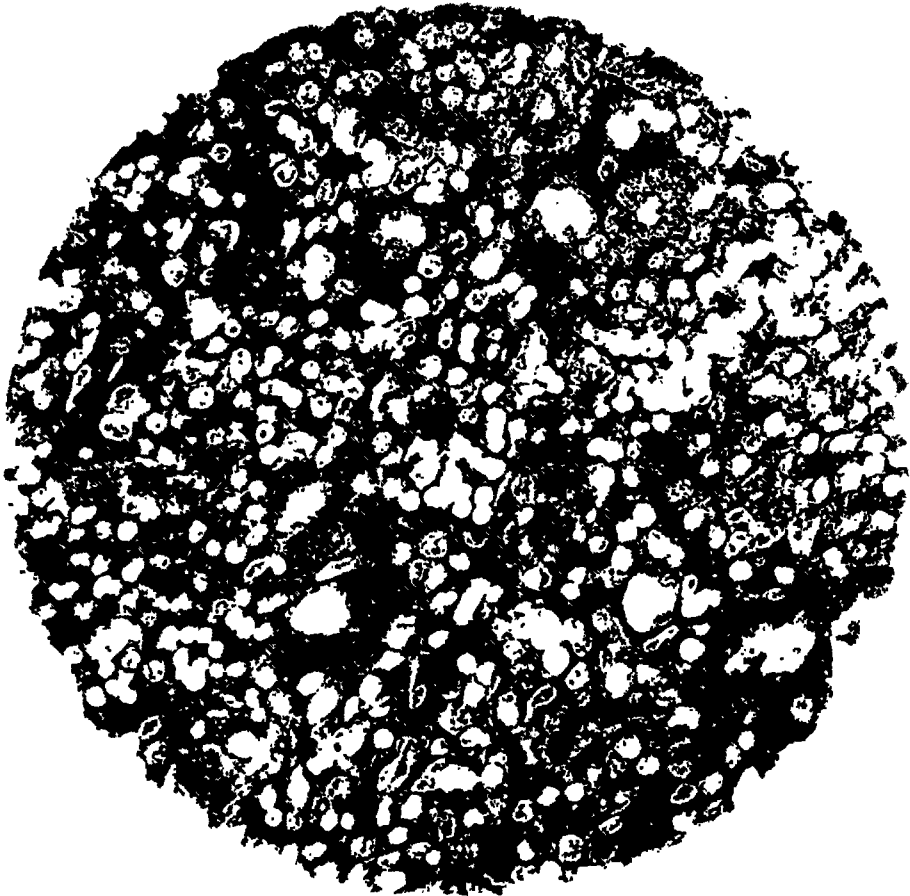
FIG. 3. Giant cells in spleen. Magnification 313.5 ×.

were loosely cellular and variable. Some spaces contained elongated marrow cells. There were a small number of multinucleated giant cells with hyperchromatic nuclei and scant cytoplasm. These cells resembled those seen in the spleen but were smaller. The remainder of the cells were myeloid, erythroid and lymphocyte-like. Moderate hematopoiesis was found; metamyelocytes and polymorphonuclears were scant. Many normoblasts were seen. Vertebrae: structure was similar to that of rib. Multinucleated giant cells were present in larger numbers; matting of elongated marrow cells was more prominent; there were many normoblasts.

Femur (figure 4) : upper end of shaft resembled section from rib and vertebrae. Minor differences were: fewer giant cells, less cellularity of marrow spaces, more prominence of fat in some of the spaces. A few small islets of dense cellular collections similar in appearance to the type of cells above described were found. Bony trabeculae were irregular, conspicuous, thicker and quantitatively increased.
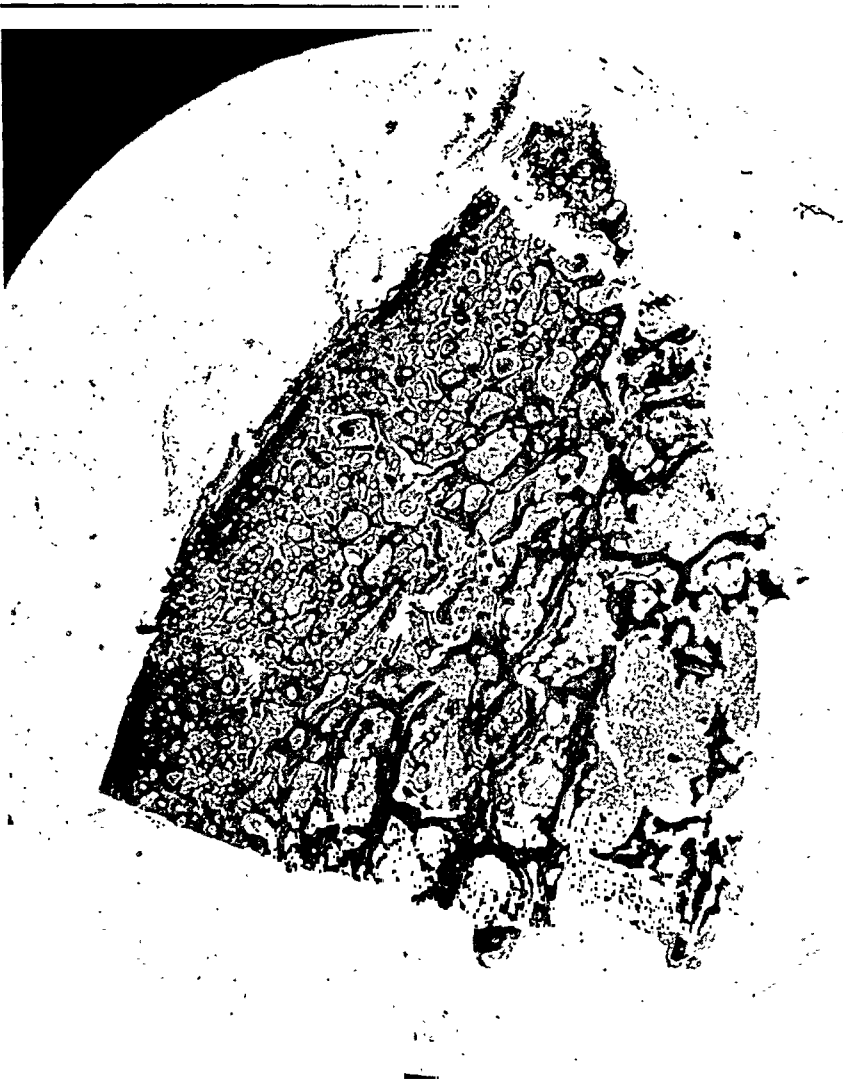
FIG. 4. Section of femur from periphery illustrating sclerosis. Magnification 6 ×.

(Figure 5) : Marrow scooped out from shaft: sections disclosed an increased cellularity invading a moderately fatty marrow. The architecture was normal but there was a preponderance of erythroid over the myeloid cells. Very few mature hematopoietic cells were seen. In some regions there was matting of the marrow cells. Some giant cells were found.

Aorta : Moderate atheroma.

Heart: Myocardium showed hypertrophy of the muscle fibers as well as marked degenerative changes. There was much separation of fibers due to edema in some

areas, and to fibrosis in others. The papillary muscles showed large areas of fibrosis as well as groups of lymphocytes and histiocytes apparently in response to myocardial degeneration.

Valves: The vegetations appeared to consist of amorphous acellular material which stained both eosinophilic and basophilic. No bacteria were found.

Kidneys: A moderate degree of degeneration of tubular epithelium was present.

Fig. 5. Section of marrow scooped out of femur illustrating giant cells and cellular content. Magnification 110 ×.

No fat or anisotropic material was found in them. The glomeruli were well preserved. Only a rare sclerotic arteriole was seen. The medulla showed a slight degree of round cell infiltration.

In the liver numerous small areas of hemorrhagic necrosis were present. Parenchymal cells were shrunken and degenerated. Many contained large quantities of brown pigment which gave the blue reaction for iron. There was a marked increase of fibrous tissue about the portal spaces and between the lobules. Numerous small foci of lymphocytes were seen, particularly in relation to the areas of fibrosis. Some fatty degeneration was present. Rare islets of hematopoiesis were seen.

Lymph nodes (figure 6) (Cervical, mediastinal, bronchial, perigastric, peri-aortic and retroperitoneal); The histological changes of the enlarged lymph nodes were essentially similar. The architecture was considerably distorted so that only an occasional follicle persisted. Those which were present did not have germinal centers. The contents of the nodes were partitioned by connective tissue trabeculae. The most common cell present was the small lymphocyte. The outstanding abnormal feature
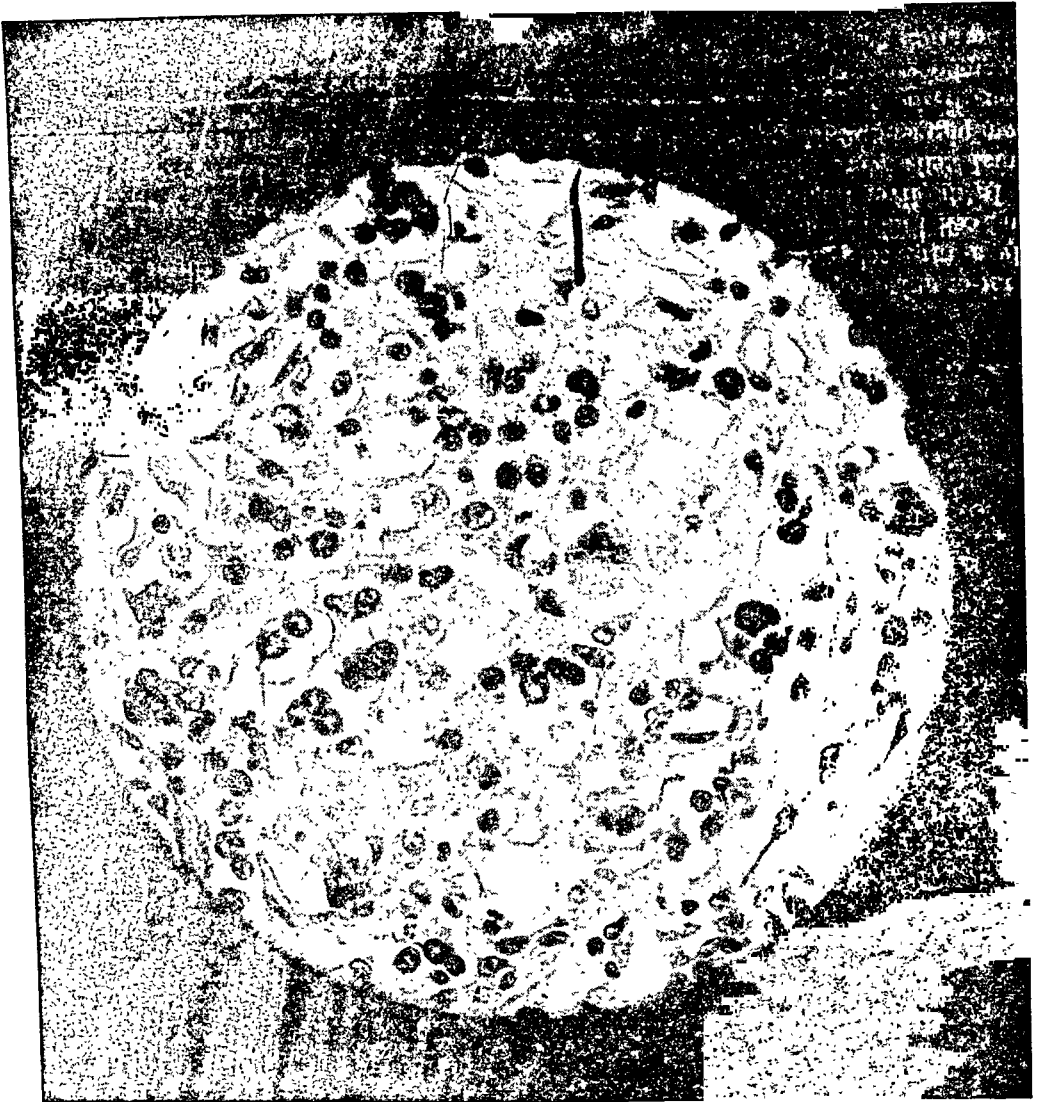
FIG. 6. Typical lymph node illustrating giant cells and architectural disorganization. Magnification 313.5 ×.

was the presence of numerous polymorphous giant cells. These were of several varieties. There were some which were mononuclear, the nucleus being monstrous, intensely basophilic in some cells and vesicular in others. The cytoplasm was distinct and usually eosinophilic. The shape of the cell was irregular. Some of these cells showed phagocytosis of erythrocytes and small lymphocytes. Other giant cells were multinuclear. Of this variety some contained many heaped up vesicular oval nuclei in

their centers; others, which were less frequent, disclosed a peripheral arrangement of nuclei. There was marked variation in the size of all the giant cells. The lymph nodes also contained many phagocytes and histiocytes. The former were loaded with a fine brown pigment which gave a blue stain for iron. Capillaries and sinuses were distinct and thin walled. The blood vessels showed no abnormalities. Scant hematopoiesis was present. The several varieties of giant cells were more numerous in the small and medium sized lymph nodes than in the large ones. The perilymphatic adipose tissue contained a moderate lymphocytic infiltrate.

Lung: There was moderate atelectasis with collapse of the alveoli. The capillaries in the walls were engorged with erythrocytes. Occasional heart failure cells were present in the alveoli.

Pancreas: The parenchymal cells contained a moderate amount of brown pigment which appeared blue when stained for iron. The cells at the periphery of the lobules appeared atrophied.

Pituitary: There were no marked abnormalities.

Histological Diagnosis: *Blood:* Leukoerythroblastic anemia. *Liver:* Hepatomegaly, cirrhosis, hemosiderosis, hemorrhagic necrosis, extramedullary hematopoiesis. *Skeletal:* Osteosclerosis—diffuse; giant cell hyperplasia. *Lymph Nodes:* Giant cell hyperplasia, hemosiderosis, extramedullary hematopoiesis. *Heart:* Hypertrophy; myocardial degeneration and fibrosis; terminal endocarditis, mitral and aortic valves; pericardial effusion. *Lungs:* Pulmonary edema, atelectasis, congestion, hydrothorax, bilateral. *Pancreas:* Hemosiderosis. *Additional:* Hydrocele, ascites, general anasarca. *Spleen:* Splenomegaly (splenectomy), multiple infarcts, giant cell hyperplasia, myeloid hyperplasia, hemosiderosis, extramedullary hematopoiesis.

DISCUSSION

An examination of the literature for cases of leukoerythroblastic anemia and osteosclerosis reveals that these symptom complexes may occur either alone or together. Furthermore, they may either be associated with other disease complexes or may occur without relationship to any other known disease. The entire situation is complicated by the unknown etiology of most of these various states.

In the differential diagnoses for osteosclerosis, the following diseases must be considered:

Albers-Schoenberg disease presents itself as an outstanding condition characterized by diffuse osteosclerosis. However, not all the cases show hematological disturbances. Some are reported associated with moderate to severe anemia, others contain descriptions of leukoerythroblastic anemia and still others have no anemia. The disease occurs in a young age group, and a history of consanguinity is occasionally present. The etiology is entirely obscure. Where both occur, it has not been possible to establish the precedence of either osseous or hematologic change.

Cases of Hodgkin's disease of the skeletal system exclusive of lymph node involvement have been reported only by E. B. Krumbhaar and another by S. K. Livingston, the former case having an anemia, whereas in the latter the blood picture was normal. However, roentgenographic changes of the bones in Livingston's case were described as rarefaction and osteolysis, resembling metastatic neoplastic disease. In our case, the bone lesions were diffuse rather than infiltrative, there being no single bone focus that could be described as discrete.

Generalized osteosclerosis has been described in cases of chronic fluorine intoxication among workers in a Copenhagen cryolite factory. The cases are too few to warrant a definite conclusion.

The association of osteosclerosis with various blood dyscrasias is more complex. The following disease states have been reported to be associated with such bony changes: chronic myelogenous leukemia, chronic lymphatic leukemia, multiple myeloma, polycythemia vera, and aplastic anemia. J. M. Vaughn and C. O. Harrison describe a case of a female 43 years of age who had had polycythemia in the past and splenomegaly of seven years' duration. Her polycythemia was followed by a leukoerythroblastic anemia and at autopsy osteosclerosis was found to be present.

The situation as regards aplastic anemia associated with osteosclerosis has been analyzed by C. P. Rhoads and D. K. Miller. In an analysis of idiopathic progressive anemia (not responding to any known hemopoietic agents) they distinguished five subgroups from histological examination of the bone marrow: (1) aplastic anemia with aplastic marrow; (2) aplastic anemia with hyperplastic marrow; (3) aplastic anemia with active marrow; (4) aplastic megakaryocytic marrow; (5) aplastic anemia with sclerotic marrow. More recently C. P. Rhoads has substituted the name of primary refractory anemia for aplastic anemia. He also points out that the various subgroups cannot be sharply defined, some cases being intermediate, and that marrow biopsy revealed one type whereas autopsy on the same case revealed another type of pathologic lesion. He urges that too much significance should not be placed on the classification into independent types.

According to this classification, our case, although not one of aplastic anemia and not strictly fitting into any one of the subdivisions, could simply be considered as one of refractory anemia with osteosclerosis.

COMMENT

The disease occurred in a male 50 years of age, ran a continuous progressive course for seven years and did not respond to splenectomy, liver or iron therapy. Ninety-five transfusions which were given during his illness appeared only to prolong life but had no effect on the disease. During the fifth year of his illness, he experienced a severe hemorrhage following the removal of a loose tooth. Three months later he had spontaneous hemorrhages from the gums. With present means of study, it is apparent that the hematological changes preceded the bone changes, since early skeletal roentgenographic examinations were negative and osteosclerosis was only discovered during his last hospital admission.

The peripheral blood changes were characterized by a severe normochromic normocytic anemia. Color index varied between 1.0, 0.9 and 0.8. Volume index was reported as .94 and mean corpuscular volume as 90. On two occasions the leukocytes (early in the course of the disease) were reported at 44,810 and 80,000. Subsequently they varied between 13,300 and 5,600, reaching the lower levels in the late stages of the disease. A leukoerythroblastic peripheral blood smear was consistently present. Terminally the platelets were 110,000. No abnormal platelets were seen.

The presence of a leukoerythroblastic picture is interesting. A case manifesting this feature was recently described by Carpenter-Flory. The authors also present an excellent summary of the literature.

1. Severe acidosis and diabetic coma: A large number of cases while in diabetic coma temporarily present the picture of relative insulin resistance according to the above definition. A few comatose cases have been reported in which unusually large doses of insulin failed to exert any appreciable effect (Thannhauser and Fuld [44]; Adlersberg and Porges [1]). They seemingly represented cases of absolute insulin resistance. Recent experience makes it doubtful whether this failure should be attributed to the ineffectiveness of insulin. Observations made by Falta [18] and by Root and Riseman [41] suggest that the expected insulin effect can be restored when doses of fluids and salts are given which far exceed those usually effective in the treatment of diabetic coma.

2. Infections: It is a common experience that infections frequently necessitate an increase in the dose of insulin and that with the drop of temperature and the disappearance of the other signs of infection the amount of insulin can be reduced to that used before the onset of the complication. Chronic infectious diseases occasionally require unusually large doses of insulin over a considerable period of time. Mohler and Goldburgh,[37] e.g., gave a patient with tuberculosis and other complications 16,515 units in 40 days. The maximum 24-hour dose of insulin in this case was 1150 units to metabolize 92 gm. of carbohydrate (corresponding to a carbohydrate equivalent of 0.08 gm.). Other remarkable cases in which infections were thought to be responsible for the development of insulin resistance have been reported by Depisch and Hasenoehrl [14] and by Byworth.[10] The observations of Wayburn [47] on a tuberculous diabetic deserve to be mentioned also. In spite of the administration of 415 units in 24 hours, this patient excreted as much as 122 gm. sugar. Therefore, it was assumed that insulin was more or less without effect and the dose was reduced to 70 units a day. This, however, was followed by coma and death. Once more the question arises as to how much the breakdown of the water and electrolyte metabolism and the anorexia in diabetics with fever may hamper the effectiveness of insulin. It is quite possible that the "insulin resistance" in many of these cases could be obviated by a treatment which aims to restore normal electrolyte, fluid and carbohydrate balances.

3. Diseases of the endocrine glands other than the pancreas: Reduced effectiveness of insulin may be expected when hyperglycemia and glycosuria are primarily due to diseases of endocrine glands other than the pancreas. This is known to occur in hyperthyroidism, in acromegaly and in pituitary basophilism.[13] Nevertheless, reports of instances in which very large doses of insulin were used with little or no effect are surprisingly scarce. On the contrary, Yater [50] found in six cases of acromegaly and diabetes studied at the Mayo Clinic that "the response to insulin was just as striking as in any cases of diabetes." Speaking of the inhibition of insulin action, Ulrich [45] pointed out that "there are gradations of antagonism in different patients with hyperpituitary disease, ranging from none at all . . . to almost complete inhibition . . ." and supports the latter statement with observations of his own. A patient of Hills, Sharpe and Gay [26] required increasing doses of insulin up to 890 units in 24 hours following thyroidectomy. However, several other complications in this case make it difficult to judge whether the change in the thyroid condition can be held solely responsible for the development of the insulin resistance. Altschuler and Gould [6] reported a case refractory to insulin in which the autopsy revealed a

large suprasellar cystic hematoma compressing the hypothalamic structures, in-
cluding the anterior and posterior lobes of the hypophysis. Unfortunately the
clinical observations are not quite conclusive.

4. *Diseases of pancreas and liver:* In contradistinction to the last group,
a few cases which, without reserve, may be called insulin resistant result
from destructive processes of the pancreas and liver. Several instances of
insulin resistance were observed in hemochromatosis. The case of Root,[39] in
which the autopsy showed hemochromatosis, called for increasing amounts of
insulin. Shortly before death 1680 units of insulin a day were given. The
patient of Wood and Fitz-Hugh [49] revealed a blood sugar constantly in the vi-
cinity of 200 mg. per 100 c.c. on a diet of 100 gm. carbohydrates and 175 units of
insulin a day. Increasing the dose of insulin had little if any effect. The pa-
tient finally died from a ruptured duodenal ulcer. Autopsy disclosed the typical
findings of hemochromatosis. In another case of hemochromatosis verified
by autopsy, Allan and Constam [3] gave up to 500 units of insulin a day. This
type of response seems to be the exception. Most cases of bronzed diabetes
usually respond well to insulin. They occasionally show, as Althausen and
Kerr [5] first described, even high sensitivity to insulin with a tendency to insulin
reactions. In a case of "acute hepatitis" reported by Root,[40] 510 units were
necessary to lower the blood sugar from 1,290 to 420 mg. per 100 c.c. within six
hours.

It is difficult to decide where the observations of Mason [34] should be classified.
The patient, during the last eight months of life, required from 200 to 400 units
of insulin a day, and finally the administration of 2,075 units in 24 hours be-
came necessary. The autopsy disclosed, besides a very small fibrotic pancreas
containing advanced calcareous degeneration, a cyst in the ventral part of the
midbrain.

It is doubtful whether the case of Pollack and Long [38] can be classified
as truly insulin resistant. In this patient the injection of 540 units of insulin
in 24 hours led to a severe hypoglycemic reaction. Autopsy revealed recent
thrombotic occlusion of all branches of the celiac artery.

Increased insulin tolerance in cases of jaundice was noted by Boller and
Ueberrack.[8] None of their cases showed true insulin resistance. Passive con-
gestion of the liver may be one factor in the increased demand of insulin in cases
of cardiac failure.

5. *Pathological changes of the skin:* It seems that at times certain skin mani-
festations interfere with the prompt action of insulin. Cases of insulin resistance
due to allergic reactions are reported (Allan and Scherer,[4] Williams,[48]
Foerster [21]). The most impressive among these cases is the one described and
discussed by Rudy.[42] Coincidental with urticaria his patient needed 515 units
of insulin with a carbohydrate intake of about 200 gm.

6. *Insulin resistance without demonstrable cause:* In several cases of insulin
resistance no reason could be demonstrated. Marble [35] recently published his
experiences with a patient whom he had followed for about three years and
whose diabetes continues to be well controlled. Her insulin requirement varied
from 240 to 675 units in 24 hours, protamine insulin forming considerable
fractions of this dose at certain times. Complications noted in this case were
severe rheumatoid arthritis, general glandular enlargement, slight to moderate

hepatomegaly and splenomegaly, and eosinophilia. Frequently quoted observations are those of Glassberg, Somogyi and Taussig.[22]   They gave a patient 26,965 units in less than three months.   The carbohydrate equivalents ranged from 0.3 to 0.7 gm.   At times there were allergic reactions to insulin, but the insulin resistance continued through periods when no such reactions were noted. Karr, Scull and Petty [31] reported a case with allergic skin reactions and insulin resistance.   On one occasion as many as 600 units of insulin were required. They also felt that in their patient both abnormalities were independent.   Although it does not seem very likely, there may be still some doubt whether the allergic skin reactions were contributory to the development of insulin resistance in the two cases just cited.`   However, there is no mention of skin reactions in the patient of Clay and Lawrence.[11]   In spite of the fact that insulin was given in increasing amounts up to 960 units per day, "no demonstrable insulin action took place" and the patient died.   At autopsy none of the conditions which occasionally cause insulin resistance could be demonstrated.

This review of the literature refers only to outstanding cases of insulin resistance, and those which throw some light on the problem.   I should like to add a report of another case which revealed several unusual features.   This patient was under my observation in the Medical Clinic of the University of Leipzig, Germany, from June 1929 to April 1932 and was briefly presented before the Medical Society of Leipzig.[43]

CASE REPORT

G. H., female, born July 26, 1912, was admitted to the Ward for Metabolic Diseases on four occasions.

First admission. In December 1928, following pharyngitis, she noticed fatigue, a feeling of heaviness in the extremities, polydipsia and polyuria.   There was polyphagia of moderate degree, pruritus, diminution of vision and loss of weight (7.5 kg. in eight weeks).   About six weeks previous to admission she had occasional pain in the upper abdomen and in the left side of the chest.   About one week before admission she developed small furuncles of the neck and the back.

Past history and family history were not contributory.   Catamenia had been regular since the age of 14 years, but there had been amenorrhea for the previous 12 weeks.

On physical examination the patient was a well developed, well nourished, almost robust female.   Height 157 cm., weight on admission 56.7 kg., on discharge 58.5 kg. There was a slight acetonemic fetor to the breath.   Both eyes showed incipient cataracts.   Teeth were in good condition. ·Tonsils were small and cryptic.   There were several hyperemic scars of recently healed furuncles on the back.   The breasts were well developed.   Chest, heart and lungs were without pathological findings. Pulse rate 80.   Blood pressure was 120 mm. Hg systolic and 85 mm. diastolic.   There was slight tenderness on light palpation in the right upper abdomen, but hepatic and splenic dullness were within normal limits.   Genitalia were normally developed. There was erythema of the vulva.   Scar of a healed furuncle on the left thigh.   The neurological examination was entirely negative.   Blood sedimentation rate was normal.   Wassermann, Kahn and Sachs-Georgi tests were negative.

During the first 24 hours patient's carbohydrate (CHO) intake was 100 gm. with 20 units of insulin before breakfast and 20 units before supper.   The urine contained 42 gm. of sugar in 24 hours.   Ferric chloride and sodium nitroprusside tests were positive; fasting blood sugar 274 mg. per 100 c.c.   Within the next 24 hours the

acetone bodies disappeared from the urine, and at the end of three days sugar was absent. Insulin could be reduced to 15 units before breakfast and 15 units before supper and the fasting blood sugar dropped to 155 mg. per cent. Gradually the CHO intake could be increased to 170 gm., and 10 days after admission the insulin requirement was 10 + 10 units. Eleven days after admission the patient developed fever with a peak of 102.8°. F. The temperature became normal within 48 hours and the fever was unexplained. Finally insulin could be discontinued entirely and the patient was sugar free on a diet consisting of 200 gm. CHO, 60 gm. protein (P), and 170 gm. of fat (F), totalling about 2600 calories. The last fasting blood sugar determined was 173 mg. per cent and the daily urine volumes averaged between 2000 and 3000 c.c.

Second admission, April 13 to July 16, 1930. Weight on admission 55 kg., on discharge 68.4 kg. Following discharge from the hospital the patient felt fairly well until Christmas 1929, when she again began to develop polydipsia and polyuria with a feeling of fatigue and general weakness. In January 1930 she had a furuncle of the gluteal region, and required 30 units of insulin a day. This could be discontinued after a few weeks. During the night of April 10, the patient vomited repeatedly.

The only changes on physical examination were acutely inflamed tonsils, scattered moist râles over the right lung, and a large deep furuncle of the right gluteal region which was about 4 to 6 cm. in diameter and exuded thick yellow pus. The temperature was elevated for the first 12 hospital days, rising to 104° F. on the tenth day. Roentgenographic examination of the chest was negative. Hemoglobin was 95 per cent; red blood cells 4,700,000; white blood cells 18,600. Smears were not remarkable.

During the first 18 hours after admission all urine tests showed strongly positive reactions with ferric chloride and sodium nitroprusside. The total food intake was 76 gm. CHO, 5 gm. P, and 3 gm. F. The total amount of insulin was 125 units and the total sugar output was 71 gm. Fasting blood sugar was 265 mg. per cent.

The urine gradually became sugar free. Thirteen days after admission, i.e., the day the temperature returned to normal, the patient tolerated a diet consisting of 100 gm. CHO, 75 gm. P, and 65 gm. F with 35 + 20 + 25 + 10 = 90 units of insulin, at 6 and 11 a.m. and 5 and 9 p.m. respectively. There was slight pitting edema which disappeared with the reduction of the insulin dose.

Four weeks after admission the furuncle had healed. The urine was sugar free. The food intake amounted to 85 gm. CHO, 75 gm. P, and 110 gm. F. Insulin was given—30 units at 6 a.m. and 25 units at 6 p.m. Fasting blood sugar was 133 mg. per cent. On July 16 she was discharged on a diet of 80 gm. CHO, 70 gm. P, and 110 gm. F with 45 units of insulin in two injections. The fasting blood sugar on the day of discharge was 184 mg. per cent, hemoglobin 95 per cent, red blood count 4,700,000, and white blood count 7,300.

Third admission (in coma) September 19, 1930 to March 14, 1931. Weight four days after admission 61.7 kg., on discharge 74 kg. The patient claimed that she adhered to her diet and insulin dosage during the months that had intervened since her discharge. Regular urine examinations showed negative sugar tests most of the time.

On September 17 the patient complained of fatigue and felt feverish. On September 18 she developed pain in the left thigh, and the family physician found a large tender hyperemic area. This was treated with alcohol compresses for 24 hours. On September 19 an abscess of the described area was incised under ether anesthesia. In the afternoon of the same day she was drowsy and vomited several times. Late in the afternoon she became comatose.

On admission to the hospital she was unconscious, with an intense acetonemic odor, dry skin, soft eyeballs, Kussmaul respiration, etc. Temperature was 101.3° F.,

pulse 124, blood pressure 90 mm. Hg systolic and 60 mm. diastolic. White blood count 17,200. There was a purulent crater about 2 cm. in diameter and 0.5 cm. in depth on the left thigh. Urine examinations showed strongly positive tests with ferric chloride and sodium nitroprusside. The urine sugar concentrations ranged from 1.5 per cent to 5.3 per cent. The patient responded to the usual coma régime and was sugar free on the fourth day. On this day her diet consisted of 70 gm. CHO, 45 gm. P, and 60 gm. F. 30 + 20 + 20 = 70 units of insulin were injected at 6 and 12 a.m. and 6 p.m. respectively. Fasting blood sugar was 353 mg. per cent. The fever gradually subsided and the dose of insulin finally could be reduced to 25 units before breakfast and 25 units before supper. In the latter part of October she experienced a rather severe tonsillitis. Following recovery she was never completely sugar free on an adequate CHO intake and doses of insulin from 40 to 50 units a day. Fasting blood sugar ranged from 187 to 320 mg. per cent.

Tonsillectomy was performed on December 1; the recovery was uneventful. On January 1, 1931 patient was on a diet of 60 gm. CHO, 80 gm. P, and 90 gm. F. The insulin dose was 40 + 15 + 40 = 95 units. The sugar output amounted to 36 gm. and the fasting blood sugar was 317 mg. per cent. Her temperature was within normal limits. By the end of the month 55 + 10 + 5 units of insulin were necessary to keep the urine almost sugar free on a diet of 75 gm. CHO, 90 gm. P and 70 gm. F. The fasting blood sugar averaged about 190 mg. per cent. Reduction of the CHO intake to 30 gm. in 24 hours without insulin was followed by aglycosuria and the fasting blood sugar fell to a normal level.

From January 28 until February 22, the temperature was elevated occasionally and at one time (February 4) reached 104.9° F. The source of the fever could not be discovered. On one occasion there was tenderness on pressure over the twelfth dorsal and first lumbar spinous processes. Roentgenographic examinations of the complete spinal column were negative. On two occasions a few leukocytes were found in catheterized specimens and urine cultures showed growth of enterococci. Specimens collected from both ureters separately, however, proved to be sterile and showed nothing but a few leukocytes. Urine cultures for tubercle bacilli and guinea pig inoculations were negative. Stool examinations did not disclose any abnormal findings. Flat plates of the abdomen, pyelograms, gastrointestinal series and roentgenographic examinations of the lungs did not suggest any pathological changes. Pelvic examination failed to reveal any findings that might be considered the cause of the fever.

Repeated basal metabolism determinations showed normal values. Roentgenographic examination of the skull and lumbar puncture did not suggest a lesion of the brain. During the last 10 days in the hospital the fasting blood sugar dropped from 241 to 169 mg. per cent. After being afebrile for more than two weeks the patient was discharged. At this time her diet consisted of 60 gm. CHO, 80 gm. P, and 80 gm. F. Even with 50 + 25 + 30 = 105 units of insulin there was a trace of sugar in each specimen but the total amount of glucose within 24 hours never exceeded 2 gm.

Fourth admission. June 28, 1931 to April 10, 1932. Weight on admission, 61.4 kg., on discharge 64.6 kg. Following discharge from the hospital the family physician decreased the daily amount of insulin 95 units. Elevations of temperature were observed several times during the first two weeks at home. She was never entirely sugar free. Subjectively she felt so well that she was able to go back to work. On the day previous to the fourth admission while shopping she developed air hunger and vomited. She was unable to walk home and was brought to the hospital by ambulance.

On admission the temperature was found to be 101.8° F. Pulse was 124, and respiration of the Kussmaul type. There was a marked acetonemic fetor, ocular tension was normal and leukocytes 10,400. There was intense redness of the pharyn-

TABLE I

Observations Made at Time of Fourth Admission for 280 Days (Figures Represent Averages of 10 Day Periods)

Date	Insulin Urine Output				Weight kg.	Fasting Blood Sugar mg. per 100 c.c.	Intake				Notes
	Units	Number of Injections	Glucose grams	N×6.25 grams			CHO gm.	Prot. gm.	Fat gm.	Calories	
7/ 1– 7/10	124.5	3.5	134.1		63.2	359	49	50	54	908	Elevated temperatures until July 2
7/11– 7/20	290.5	4.3	133.6		63.3	555	45	53	48	848	Subjectively improved; gets up for 1–2 hours
7/21– 7/30	160.0	1.5	194.0	54.7	63.6	646	42	71	42	854	General condition improved
7/31– 8/ 9	224.5	4.3	241.9	62.1	62.5	834	76	29	63	1016	Condition same
8/10– 8/19	469.0	13.6	258.2	77.0	63.7	610	100	52	59	1172	Laryngitis and bronchitis; elevated temperatures from Aug. 15 to 17. Highest temperature Aug. 16: 103.6° F.
8/20– 8/29	495.5	12.8	340.6	115.4	62.3	594	122	51	50	1174	Rise in temperature August 23–24; highest temperature 101.8° F. Bed rest
8/30– 9/ 8	353.0	11.9	256.3	79.7	65.1	486	91	44	43	953	Feels better; bed rest
9/ 9– 9/18	295.5	9.8	297.8	104.9	63.7	406	73	37	50	916	Occasional elevated temperatures; bed rest
9/19– 9/28	366.0	10.1	294.8	82.3	63.5	415	109	84	60	1349	Gets up. Fatigue and weakness
9/29–10/ 8	397.0	14.0	104.0	91.5	59.8	345*	55	37	90	1214	10/1 to 10/5: Catamenia. General ill feeling. Tachycardia, cyanosis, loss of appetite; furuncle of both labia majora. 10/6—temperature 102.5° F., and W.B.C. 11,000
10/ 9–10/18	600.0	17.0	92.3	100.1		345*	41	56	116	1476	Furuncle of left labium majus. Fever maximum 10/17, 105.2° F. W.B.C. 9,600
10/19–10/28	226.0	6.2	47.8	48.6		130	50	66	130	1684	Furuncles in both gluteal regions. Temperature elevation to 102.7° F.

TABLE I—(Continued)

Date	Insulin Urine Output						Intake				Notes
	Units	Number of Injections	Glucose grams	N ×6.25 grams	Weight kg.	Fasting Blood Sugar mg. per 100 c.c.	CHO gm.	Prot. gm.	Fat gm.	Calories	
10/29–11/7	210.0	6.0	58.7	54.6	62.6	145	57	73	144	1872	Furuncles healed. Temperature normal. Generally improved. Sits up
11/8–11/17	266.0	9.8	14.8	48.3	64.1	260	56	71	146	1878	Improved
11/18–11/27	228.0	8.7	66.5	61.0	64.7	376	52	74	139	1809	Feels fairly well
11/28–12/7	407.0	14.1	134.7	62.5	64.4	438*	46	64	120	1567	Furuncle left thigh. Continuous high temperatures since December 1
12/8–12/17	495.0	17.1	146.4	64.0	65.2	340*	43	64	123	1582	Furuncle. Temperatures still elevated
12/18–12/27	540.0	18.3	157.9	50.7	66.3	331*	52	69	131	1714	Furuncle healed; temperatures normal. Feels fairly well
12/28–1/6	463.0	17.0	192.9	71.2	65.7	423*	55	78	138	1828	Complaining of general weakness
1/7–1/16	473.5	15.2	114.7	59.2	65.1	332*	81	64	106	1580	1/12—Comatose for a few hours; 50 units of insulin intravenously. Menstruation 1/11–12
1/17–1/26	438.5	14.2	105.3	72.3	62.1	289*	87	65	107	1618	1/25—Comatose; 100 units of insulin intravenously
1/27–2/5	358.0	8.2	50.0	51.3	62.9	479	150	83	47	1392	Improved on diet comparatively high in CHO
2/6–2/15	400.0	8.8	73.4	23.4	61.9	493	140	89	64	1534	Complains of tiredness and weakness. Objectively rather alert
2/16–2/25	536.0	10.4	145.1	47.0	62.2	299	170	72	35	1358	Furuncle left upper leg. Fever since 2/22
2/26–3/6	656.0	11.7	171.7	59.3	59.6	488	159	86	43	1404	Fever continues until 2/29
3/7–3/16	1079.0	12.6	170.9	76.0	56.8	310	155	53	27	1103	Catamenia March 13–17; no fever
3/17–3/26	970.0	11.7	129.7	65.4	55.0	433	82	58	123	1717	Feeling comparatively well. Furuncles healed; no fever
3/27–4/5	970.0	10.9	104.9	52.3	54.7	323	134	82	102	1834	Urine contains leukocytes, rare hyaline casts and epithelial cells. No fever

* Indicates that the fasting blood sugar was taken less than five hours after the injection of insulin.

geal mucosa, and of the vocal cords. There were numerous rather coarse râles over both lower lobes of the lungs. The liver was palpable, firm and slightly tender. Splenic dullness was within normal limits. There was tenderness on pressure over the deep muscles of the back. Treatment for impending coma was immediately instituted. During the following three or four days it was recognized that very large doses of insulin were almost or entirely ineffective.

Table 1 summarizes observations made from July 1, 1931 until April 5, 1932. In order to save space and to enhance the clearness, the figures are given in averages of 10 day periods. For instance, the grams of glucose excreted during 10 succeeding days have been totaled and then divided by 10, etc. This obscures certain details, but significant ones will be considered later. The table does not include the first three days since they were devoted to the treatment of the impending coma and to attempts to institute a maintenance diet and a maintenance dose of insulin. The last five days of the hospital stay were given to special studies and, therefore, are omitted.

The glucose concentration in the urine was determined with the polarimeter after removal of the β oxybutyric acid. Blood sugar examinations were carried out with the micro-method of Hagedorn and Jensen.[23, 24] The original method using 0.1 c.c. of blood does not permit accurate estimations of blood sugar concentrations as encountered in this case. Therefore, the determinations were made on 0.02 and 0.05 c.c. of blood, in order to bring the final concentrations within the range of the method. Carefully calibrated pipettes were used. Numerous blood sugar curves, many of them over a period of 24 hours, were taken to determine the further course of treatment. They could not be included in this paper. Nitrogen analyses were made by the macro-Kjeldahl method and their results were expressed in terms of protein (N × 6.25).

Much care had been taken to obtain accurate CHO, N, water and salt balances. In the beginning these studies seemed to indicate that the generally assumed but not proved fact of CHO formation from fat could be demonstrated in this case. It was finally discovered that the patient obtained food from relatives and possibly from other patients, which unfortunately nullified our endeavors in this direction. In spite of her denials it is quite possible that she received considerable amounts of unaccounted nourishment. Therefore, the figures given for the intake in table 1 have to be considered as food orders and are at times possibly considerably smaller than the actual intake.

Further details can be seen in table 1. It shows among other things the unusually large amounts of insulin necessary to keep this patient fairly comfortable for almost 10 months, with the exception of periods when she developed furuncles or almost fell into coma.

The patient left the hospital against medical advice. It was suggested to the family physician that 600 units of insulin be given in seven injections daily, and that their effect be checked by frequent urine examinations. The patient died at her home in diabetic coma 12 days after her discharge from the hospital. Autopsy was refused.

DISCUSSION

The patient was under our observation for a period of 22 months, 17½ of which were spent in the hospital. Table 2 summarizes briefly the course of the disease.

After the admission in June 1929 she reacted to diet and insulin like any mild juvenile diabetic. During the following admissions the amount of carbohydrate tolerated decreased, and the dose of insulin required to render the urine sugar free increased. On the fourth admission, there seemed to be no response at all to insulin. Finally it was discovered that when using excessively large doses of

TABLE II

Data Observed on Admission and on Discharge During the Four Periods of Hospitalization

No. of Admis- sion	Condition on Admission	Observations One Day After Admission					Observations One Day Before Discharge				
		CHO Intake gm.	Glyco- suria gm.	Insu- lin units	CHO Equivalent gm. per unit	Fasting B.S. mg. per 100 c.c.	CHO Intake gm.	Glyco- suria gm.	Insu- lin units	CHO Equivalent gm. per unit	Fasting B.S. mg. per 100 c.c.
1.	Mild acidosis	103	42	40	1.53	274	200	0	0	—	173
2.	Severe acidosis	111	7	60	1.73	265	74	0	45	1.65	184
3.	Coma	76	38	70	0.54	353	52	1	100	0.51	169
4.	Impending coma	74	134	80	?0	331	132	38	1000	0.09	(94*)

* B.S. 2 hours after injection of 100 units of insulin while fasting.

insulin a fraction of the ingested carbohydrate was metabolized. In spite of the very liberal use of insulin there was only one day when the urine remained sugar free for an entire 24 hour period. Studying table 1 we arrive at a few amazing figures. During 280 days the patient received 124,915 units of various brands of insulin in 3037 injections. The sugar output in the urine amounted to 42,-330 gm. (about 93 lbs.). The average insulin dose in 24 hours was 446 units, and the average number of injections 10.8. The highest fasting blood sugar was 892 mg. per cent; on this day the patient felt well. The maximal glycosuria with insulin (375 units in 10 injections) on a single day was 489.2 gm., and without insulin 535.8 gm. The maximal dose of insulin in a 24 hour period was 1630 units given in 17 injections.

It has been intimated above that a slight effect on hyperglycemia and glycosuria was obtained with very large doses of insulin. This cannot be recognized from table 1 because it was impossible to maintain the same type of treatment over a period of 10 days, or to omit insulin for such a period without endangering the patient. However observations over several days showed repeatedly that insulin had some effect although much less than might have been expected. On a constant diet the glycosuria followed roughly the dosage of insulin as shown in tables 3 and 4.

Figure 1 demonstrates similar relationships between blood sugar and insulin. In this diagram two blood sugar curves are compared, one without insulin, the other after a single injection of 500 units. The patient was fasting during the

TABLE III

Food Intake: CHO 49 gm.; P 67 gm.; F 55–65 gm.

Date	Time of Insulin Injections	Doses Units	Total Insulin Units	Glycosuria gm.
July 20	6 a.m.; 12 noon; 7 p.m.	100+50+50	200	122.2
July 21	No insulin	0	0	224.5
July 22	6 a.m.	150	150	141.7
July 23	No insulin	0	0	223.1
July 24	9 a.m.; 6 p.m.	100+100	200	123.9

TABLE IV

Food Intake: CHO 55 gm.; P 75 gm.; F 135 gm.

Date	Time of Insulin Injections	Doses Units	Total Insulin Units	Glycosuria gm.
Jan. 3	4, 6, 7, 8 9, 10, 11, 12 a.m. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 p.m.	50, 100, 20, 20 20, 20, 20, 50 20, 20, 20, 20 20, 20, 20, 20 20, 20, 20	520	159.5
Jan. 4	No insulin		0	475.2
Jan. 5	Same as Jan. 3. minus 50 units at 4 a.m.		470	215.1
Jan. 6	Same as Jan. 3	Same as Jan. 3	520	154.0
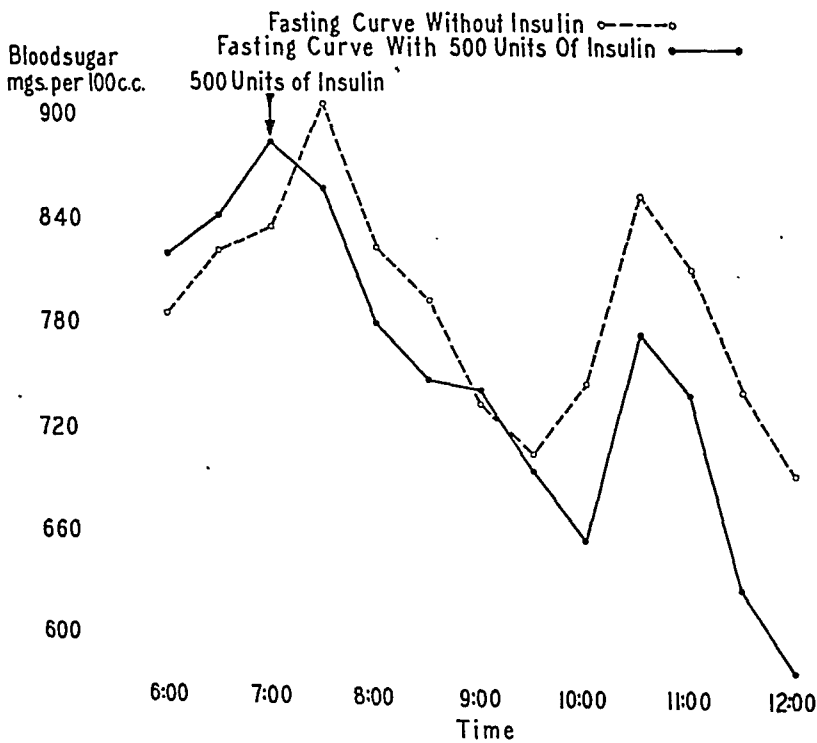
Fig. 1.

two experiments. The fasting blood sugar curve with insulin although starting from a slightly higher level runs below the fasting blood sugar curve without insulin. This difference is greater than the probable error.

These observations as well as the quoted reports from the literature, cast doubt upon the existence of absolute insulin resistance. Several unsuccessfully treated cases of insulin resistance justify the impression that increase of the already exceptionally high dose of insulin may have prevented coma and death.

There remains the question: "What was the cause of the remarkable insulin resistance in the case under discussion?" No definite explanation can be offered. There was no reason to assume greater involvement of the endocrine

glands than in other severe cases of diabetes mellitus. To be more specific, there were no signs of a macroscopic tumor of the pituitary or adrenal glands on roentgenographic examination. There were no clinical findings suggesting acromegaly or Cushing's syndrome. The basal metabolic rate was within normal limits. The menstrual disturbances did not exceed those frequently observed in poorly controlled diabetics.

The liver was palpable, enlarged and tender over a considerable period of time. Enlargement of the liver, however, has been reported as occurring rather frequently in severe cases of juvenile diabetes (Hanssen[25]; Marble et al.[36]). Functional tests practicable in diabetes did not reveal significant damage of the liver. There was no jaundice at any time, nor were the concentrations of bile and its derivatives in blood and urine abnormal. The stools were carefully studied. No undigested food residuals suggesting impairment of the external secretion of the pancreas could be discovered, although at times the diet contained large amounts of starch and particularly of fat. There were no findings to suggest the diagnosis of hemochromatosis. There was no evidence of allergic reactions, the only skin manifestations being edema while very large doses of insulin were used, and occasional furuncles.

The question of the relationship between the high fever or its causes and the insulin resistance is more difficult to decide. Most of the time the elevations of temperature were coincident with the presence of furuncles. For other short periods of fever no obvious cause could be discovered. They were thought to be due to upper respiratory infections. We are not inclined to consider these infections as the chief or even as the essential cause of the insulin resistance in the present case. First, the insulin resistance was no less at periods when the temperature, the white blood count and the blood sedimentation rate were normal and no evidence of local or general infection could be demonstrated. Secondly, intercurrent infections, especially of the skin, are of frequent occurrence in ill-controlled cases of diabetes without creating insulin resistance of such a degree. For these reasons it is our belief that our patient should be classified under the heading: "Insulin resistance without demonstrable cause."

One can only theorize as to the mechanisms underlying the phenomenon of insulin resistance, e.g., it may be that the injected insulin is not absorbed from under the skin. The observation of insulin resistance coincident with allergic skin reactions points in this direction. There is, however, no conclusive proof of this interpretation. In our case, the fact that large wheals resulting from the injection of 10 c.c. or more of insulin disappeared in a very short time would rather suggest that the rate of absorption was not abnormally slow. Somewhat related to this idea is the hypothesis that appreciable amounts of injected insulin are lost through the kidneys. Experimental evidence is against this assumption. Athanasiou and Reinwein[7] could not prove any relationship between the effectiveness of insulin and insulinuria; Glassberg and his associates[22] were unable to recover any insulin from the urine of their insulin resistant case even after the injection of 900 units within 12 hours. Root and Riseman[41] draw attention to the fact that their two patients remained anuric for several hours while unusually large doses of insulin were given and, therefore, no insulin could be lost through excretion.

Another explanation for the ineffectiveness of insulin may be the existence of

substances in the blood or in the tissues which destroy the insulin or inhibit its action. Watson and Dick [46] tested diabetic and non-diabetic urines for insulin-inhibiting substances and claimed that the urine of diabetics showed stronger inhibition of the insulin action. Karelitz and his associates [30] stated that human blood when mixed with insulin inhibits its action in rabbits. The demonstrated inactivation was greater with diabetic blood than it was with blood of normal persons. De Wesselow and Griffiths [15] found that the blood plasma of some elderly, obese, glycosuric patients, when injected into rabbits diminished the hypoglycemic action of insulin. Marble [35] saw no such effect from serum of his insulin resistant patient. In order to determine the degree of insulin inactivation produced by the blood of our patient, we thoroughly mixed 10 units of insulin with 5 c.c. of the blood and incubated the mixture for 60 minutes at 37° C. Controls of blood from normal persons were prepared in the same way. Both solutions, when injected into rabbits, produced a fast drop of blood sugar and severe insulin reactions. Looking at these experiments in retrospect we have to admit that they were incomplete. It is possible, though not likely, that with decreasing amounts of insulin a difference would have been observed between the blood of our patient and that of normal persons.

Karelitz and his co-workers [29] stated that "blood from patients with purulent infections or artificially produced infection-like conditions . . ., causes greater insulin inactivation . . . than does normal blood." They also found that "blood cells from a patient with myeloid leukemia and pus also show greater insulin inactivating power than do normal cells." They are inclined to hold an enzyme or an enzyme-like substance responsible for this fact. Zeckwer,[52] on the other hand, reports variable results as to insulin inactivation in rabbits during leukocytosis induced by sodium nucleinate. Altogether the evidence of the presence of insulin inactivating substances in the circulating blood in infectious diseases or during leukocytosis does not seem to be very conclusive.

Attempts have been made to explain the phenomenon of insulin resistance by employing certain theories which were developed to explain the normal insulin action. Although assuming different mechanisms, several students of the subject agree that insulin acts as an activator of an enzyme present in the muscles and in other tissues (Brugsch and Horsters,[9] Lundsgaard et al.,[33] Ahlgren [2]). It has been suggested that the different reactions to insulin may be due to the lack of this supposed enzyme. This idea has been expressed in a recent paper by Himsworth,[27] who thinks with others that sensitivity to insulin means lack of endogenous insulin, resistance lack of the factor which renders the insulin effective. His ideas differ from those of others inasmuch as he assumes that insulin is not the activating but the activated principle in this reaction.

Finally, it may be mentioned that within recent years another group of substances has been recognized as being antagonistic to the action of insulin. They are the hormones of the pituitary [28] and adrenal [32] glands. Cope and Marks [12] stated that a suitable extract of the anterior lobe of the pituitary gland produced resistance to insulin. Young [51] is also inclined to assume that the "insulin insensitive type of Himsworth" is due to hypersecretion of a hypophyseal factor rather than to the lack of an insulin sensitizing agent. Long [32] states that anterior pituitary extracts are effective in the absence of the pancreas, and he therefore denies the possibility that a direct neutralization of insulin is the manner by which their "diabetogenic" action is produced.

Our case and our observations do not shed any light on these interesting but still undecided problems.

SUMMARY AND CONCLUSIONS

1. The expression "insulin resistance" should be reserved for cases which require administration of at least several hundred units of insulin while on a diabetic diet and in which the carbohydrate equivalent is less than 0.5 gram.

2. Reports in the literature and our observations support the assumption that absolute insulin resistance does not occur. Even in cases which at first view seem to be absolutely insulin resistant, some insulin action can be demonstrated.

3. Therefore, insulin resistance is not an indication to discontinue the administration of insulin.

4. The case discussed progressed under our observation from a mild diabetic responding normally to insulin into a severe state of insulin resistance.

5. In the stage of insulin resistance 124,915 units of insulin were given in 3,037 injections during 280 days. In the same period 42,330 grams of sugar were excreted. The largest amount of insulin injected intramuscularly within 24 hours was 1,630 units. The highest fasting blood sugar was 892 mg. per 100 c.c.

6. In addition to certain disorders which are known occasionally to precipitate insulin resistance there are cases in which it arises from unrecognized causes.

7. The mechanisms underlying insulin resistance are still unknown.

BIBLIOGRAPHY

1. ADLERSBERG, D., and PORGES, O.: Ueber insulinrefraktaeres Coma diabeticum, Klin. Wchnschr., 1933, xii, 979.
2. AHLGREN, G.: Insulin und Glucoseverbrennung, Klin. Wchnschr., 1924, iii, 1158–1160.
3. ALLAN, F. N., and CONSTAM, G. R.: Insulin resistance in a case of bronze diabetes, Med. Clin. N. Am., 1929, xii, 1677–1687.
4. ALLAN, F. N., and SCHERER, L. R.: Insulin resistance due to allergy. With report of a case, Am. Jr. Med. Sci., 1933, clxxxv, 815–821.
5. ALTHAUSEN, T. L., and KERR, WM. J.: Hemochromatosis II. A report of 3 cases with endocrine disturbances and notes on a previously reported case. Discussion of etiology, Endocrinology, 1933, xvii, 626.
6. ALTSCHULER, S. S., and GOULD, S. E.: Diabetes refractory to insulin, with report of a case, ANN. INT. MED., 1936, ix, 1595.
7. ATHANASIOU, A., and REINWEIN, H.: Ueber exogene Insulinurie bei Zuckerkranken, Deutsch. Arch. f. klin. Med., 1931, clxxii, 307–316.
8. BOLLER, R., and UEBERRACK, K.: Die Insulintoleranz bei Faellen von Ikterus, Klin. Wchnschr., 1932, xi, 671.
9. BRUGSCH, TH., and HORSTERS, H.: Ueber die Cofermentnatur des Insulins, Ztschr. f. physiol. Chem., 1926, clvii, 186–191.
10. BYWORTH, H. A.: Massive dosage with insulin, Brit. Med. Jr., 1928, i, 801.
11. CLAY, R. D., and LAWRENCE, R. D.: An insulin-resistant diabetes, Brit. Med. Jr., 1935, vii, 697–698.
12. COPE, O., and MARKS, H. P.: Further experiments on the relation of the pituitary gland to the action of insulin and adrenaline, Jr. Physiol., 1934, lxxxiii, 157–176.
13. CUSHING, H.: Papers relating to the pituitary body, hypothalamus and parasympathetic nervous system, 1932, Charles C. Thomas, Springfield, Illinois, and Baltimore, Maryland. (Footnote p. 35.)

14. DEPISCH, F., and HASENOEHRL, R.: Experimentelle Untersuchungen ueber die Insulin-resistenz beim Diabetes mellitus, Ztschr. f. d. ges. exper. Med., 1928, lviii, 110–116.

15. DE WESSELOW, O. L. V., and GRIFFITHS, W. J.: On the possible rôle of the anterior pituitary in human diabetes, Lancet, 1936, i, 991.

16. FALTA, W.: Lebensaussichten der Diabetiker, Klin. Wchnschr., 1935, xiv, 697 and 741.

17. FALTA, W.: Theoretische Grundlagen der Diabetesbehandlung, Wien. klin. Wchnschr., 1936, xlix, 65.

18. FALTA, W.: Protamin-Zink-Insulin und Insulinresistenz, Wien. Arch. f. inn. Med., 1938, xxxii, 97–120.

19. FALTA W., and BOLLER, R.: Insulinaerer und insulinresistenter Diabetes, Klin. Wchnschr., 1931, x, 438.

20. FENZ, E.: Ueber Haeufigkeit und Besonderheiten des insulinempfindlichen und insulin-resistenten Diabetes, Klin. Wchnschr., 1936, xv, 681–683.

21. FOERSTER, E.: Ein Fall von paradoxer Insulinwirkung, Med. Klin., 1926, xxii, 846–849.

22. GLASSBERG, B. Y., SOMOGYI, M., and TAUSSIG, A. E.: Diabetes mellitus—report of a case refractory to insulin, Arch. Int. Med., 1927, xl, 676–685.

23. HAGEDORN, H. C., and JENSEN, B. N.: Die Ferricyanidmethode zur Blutzuckerbestimmung, Biochem. Ztschr., 1923, cxxxvii, 92–95.

24. HAGEDORN, H. C., and JENSEN, B. N.: Zur Mikrobestimmung des Blutzuckers mittels Ferricyanid, Biochem. Ztschr., 1923, cxxxv, 46–58.

25. HANSSEN, P.: Enlargement of the liver in diabetes mellitus, Jr. Am. Med. Assoc., 1936, cvi, 914–916.

26. HILLS, R. G., SHARPE, J. C., and GAY, L. N.: Diabetes mellitus and hyperthyroidism. The report of a case, Bull. Johns Hopkins Hosp., 1934, lv, 193–200.

27. HIMSWORTH, H. P.: Diabetes mellitus. Its differentiation into insulin-sensitive and insulin-insensitive types, Lancet, 1936, i, 127.

28. HOUSSAY, B. A.: Carbohydrate metabolism, New England Jr. Med., 1936, cxiv, 971.

29. KARELITZ, S., COHEN, P., and LEADER, S. D.: Insulin inactivation by human blood cells and plasma in vitro; effect of infection on insulin, Arch. Int. Med., 1930, xlv, 546–558.

30. KARELITZ, S., COHEN, P., and LEADER, S. D.: Insulin inactivation by human blood cells and plasma in vitro; effect of normal and of diabetic blood on insulin action, Arch. Int. Med., 1930, xlv, 690–701.

31. KARR, W. G., SCULL, C. W., and PETTY, O. H.: Insulin resistance and sensitivity, Jr. Lab. and Clin. Med., 1933, xviii, 1203.

32. LONG, C. N. H.: The influence of the pituitary and adrenal glands upon pancreatic diabetes, Harvey Lectures (1936–1937), 1937, Williams & Wilkins Co., Baltimore, pp. 194–228.

33. LUNDSGAARD, CH., and HOLBOLL, S. A.: Studies in carbohydrate metabolism II–V, Jr. Biol. Chem., 1925, lxv, 305, 323, 343, 363.

34. MASON, E. H.: The life history of a diabetic who acquired an unusual tolerance to insulin, Jr. Clin. Invest., 1930, ix, 31.

35. MARBLE, A.: Insulin resistance. Report of a case of marked insensitiveness of long duration without demonstrable cause, Arch. Int. Med., 1938, lxii, 432–446.

36. MARBLE, A., WHITE, P., BOGAN, I. K., and SMITH, R.: Enlargement of the liver in diabetic children. II. Effect of raw pancreas, betaine hydrochloride, and protamine insulin, Arch. Int. Med., 1938, lxii, 751–764.

37. MOHLER, H. K., and GOLDBURGH, H. L.: Diabetes mellitus with resistance to insulin and failure to obtain clinical improvement from its use. Report of cases, Med. Clin. N. Am., 1931, xv, 343–352.

38. POLLACK, H., and LONG, E. R.: Thrombosis of the hepatic artery with sudden resistance to insulin in a diabetic patient, Arch. Path., 1932, xiii, 530.

39. ROOT, H. F.: Insulin resistance and bronze diabetes, New England Jr. Med., 1929, cci, 201–206.

40. ROOT, H. F.: Acute hepatitis in a diabetic with severe acidosis and suppression of urine, New England Jr. Med., 1935, ccxii, 545.
41. ROOT, H. F., and RISEMAN, J. E. F.: The exceptional requirement of insulin and salt solution in diabetic coma, Jr. Am. Med. Assoc., 1938, cx, 1730.
42. RUDY, A.: Urticaria and insulin resistance with reference to the relation of the skin to the carbohydrate metabolism.—Report of a case and review of literature, New England Jr. Med., 1931, cciv, 791–796.
43. SCHLOSS, J.: Merkwuerdiger Fall von Diabetes mellitus, Klin. Wchnschr., 1932, xi, 436.
44. THANNHAUSER, S. J., and FULD, H.: Insulinmangelkoma und insulinrefraktaeres Koma im Verlaufe eines Diabetes mellitus, Klin. Wchnschr., 1933, xii, 252–258.
45. ULRICH, H.: The antagonism between insulin and pituitary extract. Its demonstration in a patient with acromegaly, Arch. Int. Med., 1928, xli, 875–882.
46. WATSON, E. M., and DICK, W. S.: Some observations concerning a possible insulin-inhibiting substance in urine, ANN. INT. MED., 1933, vi, 1171–1179.
47. WAYBURN, E.: Complete insulin resistance in diabetes, Am. Jr. Med. Sci., 1935, cxc, 157–164.
48. WILLIAMS, J. R.: Allergic insulin reactions. Report of a case exhibiting severe gastrointestinal allergic reactions following injections of insulin, Jr. Am. Med. Assoc., 1930, xciv, 1112–1114.
49. WOOD, F. C., and FITZ-HUGH, T., JR.: Hemochromatosis in a metal worker. Case report with autopsy and a brief review of the literature, Arch. Int. Med., 1929, xliv, 882–892.
50. YATER, W. M.: Acromegaly and diabetes. Report of six cases, Arch. Int. Med., 1928, xli, 883–912.
51. YOUNG, F. G.: Glycogen and the metabolism of carbohydrate, Lancet, 1936, ii, 237 and 297.
52. ZECKWER, I. T.: Resistance to insulin; response to insulin in rabbits during leucocytosis induced by sodium nucleinate, Arch. Path., 1932, xiii, 766–778.

EDITORIAL

EXTRA-HUMAN SOURCES OF POLIOMYELITIS VIRUS

ALTHOUGH the pathway of infection in poliomyelitis has long been a matter of controversy, until recently it was generally believed to be usually the nasal olfactory mucosa, the olfactory tracts and bulbs, from which the virus spreads by direct extension to the motor areas of the brain and spinal cord. Infection was thought to be acquired by droplet infection or direct contact, usually from carriers or unrecognized subclinical cases of the disease. This view has been maintained by Flexner and his associates, based largely on their studies of experimental infections in monkeys.

More recent work, however, has cast doubt on the validity of this view as far as human infection is concerned, and points strongly to the alimentary tract as the usual portal of entry of infection. Some of the more important observations on which this view is based have already been discussed.[1] As previously pointed out, there is ample proof that in many cases, at least, virus is present in the feces in large amounts, and that it can remain viable in feces and in contaminated sewage for substantial periods of time. This manifestly constitutes an important possible source of infection, if the view is confirmed that man may be infected through the gastrointestinal tract. In that event, the mode of dissemination of the disease might be expected to resemble that of typhoid fever rather than a respiratory tract infection and opportunities for fecal contamination of foods would be epidemiologically important.

The recent demonstration that flies may be carriers of the virus is, therefore, of great interest. Although several isolated successful attempts were reported in 1911 and 1912, adequate confirmation was not obtained until 1941, when Toomey et al., Paul, Trask, et al., and Sabin and Ward independently reported the demonstration of the virus in washings or emulsions of flies trapped near houses which were harboring or had recently harbored cases of the disease. Sabin and Ward [2] reported eight positive results out of 15 samples examined, and Trask, Paul and Melnick [3] obtained four positive out of 19 samples tested. In most cases the flies had access to feces which presumably may have contained virus. No evidence was obtained that the flies were more than passive carriers, nor is there evidence as yet that human cases have actually been infected from this source.

The possibility that other mammals might serve as a reservoir of infection hitherto has received little consideration because (except for the

[1] The pathway of infection in poliomyelitis, Editorial, ANN. INT. MED., 1941, xv, 329–332.

[2] SABIN, A. B., and WARD, R.: Insects and epidemiology of poliomyelitis, Science, 1942, xcv, 300.

[3] TRASK, J. D., PAUL, J. R., and MELNICK, J. L.: The detection of poliomyelitis virus in flies collected during epidemics of poliomyelitis, Jr. Exper. Med., 1943, lxxvii, 531–544 and 545–556.

monkey) the ordinary domestic and laboratory animals are usually quite resistant to inoculations of the virus. In a few cases, however, infections with certain strains of poliomyelitis virus have been established in white mice. In 1939 Armstrong was able to convey a freshly isolated human strain ("Lansing" strain) of virus from a monkey to cotton rats, and after infection was well established in the rats to carry it on in white mice. In 1940 Jungeblut and Sanders [4] were able in three different series of animals to convey the SK New Haven strain of poliomyelitis virus in a similar manner from monkeys to cotton rats, and then to white mice. In 1941 Toomey also was able to establish infection in white mice with the RMV strain of virus. These were accomplished only with much difficulty, however, and many unsuccessful attempts have been made to infect mice with other strains.

After the infection was once established in mice,[4] the virus showed some alteration as a result of its adaptation to this species. Its virulence for mice increased greatly, so that the animals could be infected by highly diluted (one to one billion) virus suspensions, and by peripheral as well as by intracerebral inoculation. They could also be infected by feeding the virus. With this increase in virulence for mice, however, there was a more or less marked reduction or even a nearly complete loss of virulence for monkeys. There were also some changes in the immunological reactions of the virus. It seemed probable, however, that the mouse-adapted strain of virus represented a variant or mutant of the original strain rather than a specifically different virus. The histological lesions produced in mice were typical of poliomyelitis and the immunological reactions indicated at least a close group relationship. These observations, however, would give no basis for the expectation that such a virus would be readily passed back and forth from mice to man.

Recent observations of Jungeblut and Dalldorf,[5] however, indicate that this possibility must receive serious consideration, at least for some strains of virus. They studied an epidemic of poliomyelitis occurring in a circumscribed area in White Plains, N. Y., and consisting of five cases of which two were fatal. In the basement of the house in which one patient had died, they found one freshly dead gray mouse, and they trapped a considerable number of live mice in this and other houses in the area. By intracerebral inoculation of albino mice they demonstrated a virus in the brains of three of the captured gray mice, including the one found dead. The affected animals showed symptoms of encephalitis which in some progressed to paralysis and death. Two of the virus strains died out, but the third (from the dead mouse) was established successfully in white mice, with increase in virulence. It also infected cotton rats and hamsters, but not rabbits, guinea pigs or rhesus monkeys. The agent was filtrable. It produced lesions in the brains

[4] JUNGEBLUT, C. W., and SANDERS, M.: Studies of a murine strain of poliomyelitis virus in cotton rats and white mice, Jr. Exper. Med., 1940, lxxii, 407–436.

[5] JUNGEBLUT, C. W., and DALLDORF, G. T.: Epidemiological and experimental observations on the possible significance of rodents in a suburban epidemic of poliomyelitis, Am. Jr. Pub. Health, 1943, xxxiii, 169–172.

of the mice identical with those caused by known strains of poliomyelitis virus. It was inactivated by the serum of the three convalescent human cases.

A virus was also isolated from the brain of one of the human cases by successive intracerebral inoculation in a monkey, a hamster, and in white mice. This virus was described as similar in all respects to the strain obtained from the gray mouse except in the higher degree of virulence which it attained. It was also neutralized by sera from the three convalescent human cases, and in varying degree by antisera to Theiler's mouse encephalomyelitis virus, to the SK murine strain of poliomyelitis virus, and to a monkey poliomyelitis virus. The authors conclude that the virus belongs to the poliomyelitis group of viruses, and is possibly related to Theiler's mouse encephalomyelitis virus.

The results of these experiments must be interpreted with caution. It seems improbable that the virus strains obtained were simply contaminants, although this is perhaps not entirely excluded. It seems highly probable that the virus strains obtained from the mice and the human case were identical. Their identity with ordinary strains of human poliomyelitis virus is much more questionable, particularly those which have resisted adaptation to mice. They do indicate the need of further intensive study of these questions, and suggest the possibility that in some cases human infection might result from the contamination of food by the excreta of infected mice.

REVIEWS

Heart Failure. By Arthur M. Fishberg, M.D., 2nd edition. 829 pages; 15.5 × 24 cm. Lea & Febiger, Philadelphia. 1940. Price, $8.50.

Incorporating advances made in the field since the first publication, the second edition of this fine book holds a vast amount of information for those interested in the cardiovascular system. The material is well ordered and clearly presented and no aspect of circulatory failure seems to be omitted. The physiologic mechanisms regulating changes in the circulation and the basis for the various symptoms and signs in failure are covered in detail. Physiology is related to clinical cardiology in the discussions of failure in various cardiac affections and in the rationalization of treatment. There is a large bibliography with well incorporated references, and the table of contents and index are full enough so that desired topics can be found. The book therefore serves as an unique reference work on circulatory failure and is highly recommended as authoritative in this field.

C. E. L.

Tables of Food Values. By Alice V. Bradley, M.S. 224 pages; 20 × 25.5 pages. The Manual Arts Press, Peoria, Ill. 1943. Price, $3.50.

This book has been completely revised, enlarged and brought up-to-date with the most recent scientific information pertaining to the nutritive value and composition of foods. It is divided into four sections.

Section I briefly and clearly discusses the most important factors in the composition of an adequate diet. The carbohydrates, fats, proteins, and body regulators (minerals, vitamins, cellulose, and water) are each explained as to composition, body requirements, and body function. Body requirements and availability of each of the essential minerals and vitamins are discussed in non-technical terms.

The second section emphasizes the points to consider in diet calculation and menu planning. A list of foods which should be included in the daily adequate diet is given. The factors which determine one's caloric requirement and the method of computing an individual's daily caloric requirement may be easily understood. Rules to be considered in planning well-balanced and tempting meals are listed with examples. A chart of the daily allowances of specific nutrients recommended by the National Nutritional Conference in Washington, D. C. in 1941 is given.

Section III consists of charts showing the food values of average servings of common foods expressed in grams and household measures. The amounts of protein, fat and carbohydrate are listed in grams, the minerals in shares, and the vitamins in Internation Units or milligrams. Recipes accompany many of the tables, such as those of cakes and ice cream.

Section IV is composed of tables showing the food values of 100 gram portions instead of average servings of the same foods in the third section. This is valuable for accurate calculation of weighed diets.

For anyone interested in the composition and nutritive values of foods or in computing diets with accuracy, this book is sufficient with no other reference necessary.

E. F.

BOOKS RECEIVED

Books received during July are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Memoir of Walter Reed. The Yellow Fever Episode. By ALBERT E. TRUBY, Brigadier General, United States Army, retired. 239 pages; 20 × 13.5 cm. 1943. Paul B. Hoeber, Inc., New York, N. Y. Price, $3.50.

Methods of Treatment. Eighth Edition. By LOGAN CLENDENING, M.D., and EDWARD H. HASHINGER, A.B., M.D. 1033 pages; 25 × 17 cm. 1943. C. V. Mosby Co., St. Louis, Missouri. Price, $10.00.

A Synopsis of Clinical Syphilis. By JAMES KIRBY HOWLES, B.S., M.D., M.M.S. 671 pages; 20 × 13.5 cm. 1943. C. V. Mosby Co., St. Louis, Missouri. Price, $6.00.

Rehabilitation of the War Injured. A Symposium. Edited by WILLIAM BROWN DOHERTY, M.D., and DAGOBERT D. RUNES, Ph.D. 684 pages; 23.5 × 16 cm. 1943. Philosophical Library, Inc., New York, N. Y. Price, $10.00.

El Pulso Venoso Normal. (Tesis de Doctorado en Medicina.) By AGUSTÍN CAEIRO. 148 pages; 23 × 16 cm. 1943. Sebastián de Amorrortu e Hijos, Buenos Aires.

Handbook of Tropical Medicine. By ALFRED C. REED, M.D., and J. C. GEIGER, M.D. 188 pages; 17 × 12 cm. 1943. Stanford University Press, Stanford University, California. Price, $1.50.

Addendum to the Chemistry of the Amino Acids and Proteins. Edited by CARL L. A. SCHMIDT, M.S., Ph.D. 1290 pages; 26 × 17 cm. 1943. Charles C. Thomas, Springfield, Illinois. Price, $5.00.

Gastro-Enterology (in three volumes). Volume I: *The Esophagus and the Stomach.* By HENRY L. BOCKUS, M.D. 831 pages; 25.5 × 17 cm. 1943. W. B. Saunders Co., Philadelphia. Price (three volumes), $35.00.

Borderlands of Psychiatry. (Harvard University Monograph in Medicine and Public Health—No. 4.) By STANLEY COBB, Bullard Professor of Neuropathology, Harvard Medical School; Psychiatrist in Chief, Massachusetts General Hospital. 166 pages; 23.5 × 16 cm. 1943. Harvard University Press, Cambridge, Massachusetts. Price, $2.50.

COLLEGE NEWS NOTES

ADDITIONAL A. C. P. MEMBERS IN THE ARMED FORCES

Already published in preceding issues of this journal were the names of 1,453 Fellows and Associates of the College on active military duty. Herewith are reported the names of 18 additional members, bringing the grand total to 1,471.

Kenneth D. A. Allen
Horace M. Banks
Asher S. Chapman
Cyrus J. Clark
William R. Galbreath
Emil H. Grieco
William E. Hall
Joseph F. Jenovese
H. Beckett Lang

Thomas A. Lebbetter
George W. Lynch
Ralph Lynch
John F. McManus
Robert S. Palmer
Lucian A. Smith
Lydon H. Thatcher
Louis D. Vaughn
Philip Work

GIFTS TO THE COLLEGE LIBRARY

We gratefully acknowledge receipt of the following gifts to the College Library of Publications by Members:

Books

Dr. Jacob C. Geiger, F.A.C.P., San Francisco, Calif.—"Handbook of Tropical Medicine."

Reprints

Dr. Guy H. Faget, F.A.C.P., U. S. Public Health Service, Carville, La.—1 reprint;
Dr. James M. Flynn, F.A.C.P., Rochester, N. Y.—1 reprint;
Irving Greenfield, F.A.C.P., Captain, (MRC), U. S. Army—1 reprint;
Dr. John F. Kenney, F.A.C.P., Pawtucket, R. I.—1 reprint;
Dr. Richard E. DeMonbrun Kepner, F.A.C.P., Honolulu, T. H.—2 reprints;
Horace Page Marvin, F.A.C.P., Lieutenant Colonel, (MC), U. S. Army—1 reprint;
Dr. Thomas H. McGavack, F.A.C.P., New York, N. Y.—1 reprint;
Dr. Frederick W. Mulsow, F.A.C.P., Cedar Rapids, Iowa—2 reprints;
Dr. William H. Ordway, F.A.C.P., Mount McGregor, N. Y.—1 reprint;
Dr. Dudley C. Smith, F.A.C.P., University, Va.—11 reprints;
Leon H. Warren (Associate), Major, (MRC), U. S. Army—1 reprint.

SCHEDULE OF EXAMINATIONS BY CERTIFYING BOARDS

AMERICAN BOARD OF INTERNAL MEDICINE:

William A. Werrell, M.D., Assistant Secretary
1301 University Ave.
Madison, Wis.

Written Examination: October 18, 1943. Will be held in various cities and may be arranged at some Army and Navy stations with the approval of medical commanding officers.

Oral Examination: Communicate with the Assistant Secretary for schedule of examinations in various parts of the country. During the war, oral examinations are held at various times in New Orleans, San Francisco, Philadelphia and other cities.

AMERICAN BOARD OF DERMATOLOGY AND
SYPHILOLOGY:
    C. Guy Lane, M.D., Secretary
    416 Marlboro St.
    Boston, Mass.
AMERICAN BOARD OF PEDIATRICS:
    C. A. Aldrich, M.D., Secretary
    707 Fullerton Ave.
    Chicago, Ill.
AMERICAN BOARD OF PSYCHIATRY AND
NEUROLOGY:
    Walter Freeman, M.D., Secretary
    1028 Connecticut Ave., N. W.
    Washington, D. C.

Written Examination: Various cities, September 27, 1943.
Oral Examination: Philadelphia, November 5–6, 1943.

Written Examination: October 8, 1943 (locally, under a monitor).
Oral Examination: New York, N. Y., November 20–21, 1943.

Written Examination: October 30, 1943, locally.
Oral Examination: December 20–21, 1943, locally. Final date for filing application, September 30, 1943.

REGIONAL MEETINGS OF THE COLLEGE

The Northwest Regional Meeting

A Regional Meeting for the states of Washington, Oregon and Idaho, and for the provinces of Alberta, British Columbia, Manitoba and Saskatchewan, will be held at Seattle, Wash., September 24, 1943, under the General Chairmanship of Dr. Edwin G. Bannick, Acting Governor for Washington, and under an Executive Committee consisting of Dr. Homer P. Rush, Governor for Oregon, Dr. Samuel M. Poindexter, Acting Governor for Idaho, and Dr. George F. Strong, Governor for the Southwestern Provinces of Canada.

The meeting will consist of clinical presentations in the morning, general sessions in the afternoon, and a dinner meeting in the evening. Meetings will be held on the University of Washington campus, where excellent facilities are available. The evening dinner meeting will be addressed by Dr. Ernest E. Irons, President-Elect, of Chicago, Brigadier General David N. W. Grant, Air Surgeon of the U. S. Army Air Forces, Washington, D. C., Brigadier General Hugh J. Morgan, of the Office of the Surgeon General, U. S. Army, Washington, D. C., Rear Admiral W. L. Mann, Commandant, Thirteenth Naval District, Seattle, Colonel Wallace Wilson, Command Medical Officer, Pacific Command, Royal Canadian Army Medical Corps, and others.

A formal program may be obtained from the Executive Offices of the College.

All medical officers of the Armed Forces of the United States and Canada are cordially invited, whether members of the College or not. The Regional Meeting of the College will be followed by a meeting the succeeding day of the North Pacific Society of Internal Medicine.

North-Central States Regional Meeting

A Regional Meeting, embracing Illinois, Indiana, Iowa, Michigan and Wisconsin, will be held at the Drake Hotel, Chicago, October 16, 1943, under the General Chairmanship of Dr. LeRoy H. Sloan, College Governor for Northern Illinois and under an Executive Committee of the Governors for the participating regions, including Dr. Cecil M. Jack, Decatur, Ill., Dr. Robert M. Moore, Indianapolis, Ind., Dr. Benjamin F. Wolverton, Cedar Rapids, Iowa, Dr. Patrick L. Ledwidge, Detroit, Mich., and Dr. Elmer L. Sevringhaus, Madison, Wis.

Formal program will be ready for distribution September 20, 1943. All medical officers of the Armed Forces, in addition to members of the College, are cordially invited.

·Chicago Regional Meetings of the College in the past have been exceptional. Attendance has been large and the programs have been of the best. It is anticipated that this meeting will be most successful.

It so happens that a postgraduate course in Endocrinology, arranged by the College under the direction of Dr. Willard O. Thompson at the Presbyterian Hospital, will be given during the preceding week, from October 11, and all physicians taking that course are invited to participate in the Regional Meeting of the College.

The Philadelphia Round-Up

The 6th Annual Regional Meeting of Eastern Pennsylvania, New Jersey, Delaware, and adjacent territory, will be held at Philadelphia, Friday, November 19, 1943, under the General Chairmanship of Commander Edward L. Bortz, (MC), U. S. Naval Reserve, College Governor for Eastern Pennsylvania, and with the assistance of the Governors of the participating regions, including Dr. George H. Lathrope, Governor for New Jersey, and Dr. Lewis B. Flinn, Governor for Delaware. The morning will be devoted to a special program arranged by Dr. O. H. Perry Pepper of the Hospital of the University of Pennsylvania, followed by a buffet luncheon at the College Headquarters at 4200 Pine St.; an afternoon general session in the ballroom of the Benjamin Franklin Hotel, Ninth and Chestnut Sts.; and an evening cocktail party-dinner meeting at the Hotel. Significant on the afternoon program will be presentations by medical officers from the Army and Navy of the United States and Canada who have had first-hand experience in the war zones and in rehabilitation and care of the wounded.

It is expected that several dignitaries from the Army and Navy, as well as from the general profession, will be on the program at the dinner meeting in the evening.

As already published in the August issue of this journal, a postgraduate course in Special Medicine will be given at Philadelphia institutions during the preceding two weeks, and the program will terminate in this Regional Meeting. Therefore, invited to the meeting are all members of the College, all registrants in the postgraduate course in Special Medicine, and all medical officers in the Armed Forces and others who may be especially interested in any feature in the program. ·

A. C. P. Postgraduate Courses

The Postgraduate Bulletin of the College, containing the list of its courses offered in the autumn, 1943, is ready for distribution. The schedule calls for the following three courses and the Bulletin gives the detailed data concerning each. Address inquiries to the Executive Secretary, 4200 Pine St., Philadelphia, Pa.

Course No. 1—Endocrinology
(October 11–16, 1943)
University of Illinois College of Medicine and the
Presbyterian Hospital
1753 W. Congress St., Chicago, Ill.
Willard O. Thompson, M.D., F.A.C.P., *Director*
Fee, $20.00

Course No. 2—Allergy
(October 25–30, 1943)
Roosevelt Hospital, New York, N. Y.
Robert A. Cooke, M.D., F.A.C.P., *Director*
(Minimal Registration, 25: Maximal Registration, 50)
Fee, $20.00

<div align="center">

COURSE No. 3—SPECIAL MEDICINE
(November 8–19, 1943)
Philadelphia Institutions
CHARLES L. BROWN, M.D., F.A.C.P., *Director*
Fee, $40.00

</div>

Colonel Edgar Erskine Hume, (MC), U. S. Army, (F.A.C.P.), has been appointed Health Officer of Occupied Sicily, in connection with the Allied Military Government of Occupied Territory.

Lieutenant Colonel Charles T. Young, (MC), U. S. Army (Associate), was awarded the Legion of Merit for exceptionally meritorious service in the performance of his duties during and after the Japanese attack on Oahu, December 7, 1941. Colonel Young was Chief of the Medical Service. The citation indicated that by his excellent judgment and thorough adaptability he reflected great credit on the Medical Corps of the U. S. Army. Colonel Young has been an Associate of the American College of Physicians since 1939.

Captain E. David Sherman, R.C.A.M.C., (Associate), Sydney, N. S., Canada, has been appointed Abstract Editor of the Nova Scotia Medical Bulletin and Consultant in Cardiology to the Marine Hospital at Sydney.

Lieutenant Mack Leonard Gottlieb, (MC), U. S. Naval Reserve, an Associate of this College, was taken prisoner at Guam and is now interned at the Zentsuji War Prison Camp, Shikoku, Japan.

The Air Medal was conferred August 4, 1943, on Major Aaron A. Sprong, (F.A.C.P.), Post Flight Surgeon at the Strother Army Air Field, Kan. Major Sprong was cited for "meritorious achievement while participating in an air flight on December 16, 1942, over the Solomon Islands. Major Sprong was Flight Surgeon for the No. 5 wingman in a successful bombing mission with a flight of six B–17 airplanes. Sixteen enemy fighters attacked the formation and the No. 3 wingman was disabled early in the encounter. No. 5 wingman remained with the injured plane until it crash-landed although he, too, had lost one engine in the encounter. The action by the No. 5 wingman helped to prevent the complete destruction and loss of No. 3 wingman from enemy action. The crew was later rescued. At least four enemy fighters were destroyed."

SCHOOL OF MILITARY GOVERNMENT ESTABLISHED AT THE UNIVERSITY OF VIRGINIA

The School of Military Government has been established, under the auspices of the Provost Marshal General's Office of the War Department, at Charlottesville, Va. It is designed to prepare officers for future detail in connection with military government and liaison.

Each class of the School is made up entirely of commissioned officers of the grades of Captain to Colonel. Applications are not considered from persons not in the military service. Students are selected by the War Department following recommendations of the Commandant and the Provost Marshal General. In evaluating qualifications, much weight is given to experience in a former military government and in the Federal Government, or in the government of a state, county or city, and to professional training in government and public administration. Importance is

attached to demonstrated administrative and executive ability and to a knowledge of foreign languages and countries.

Officers on active duty are selected from recommendations made by higher commanders and chiefs of services and others. They may also apply for admittance to the School by letter addressed to the Provost Marshall General, through proper channels. All applications should give complete information as to age, education, training and experience, both military and civilian. Inquiries concerning commissions should be directed to the nearest office of Officer Procurement Service.

Major Leon H. Warren (Associate), M.C., U. S. Army, delivered an address on Military Dermatology, July 16, to the students of George Washington University Medical School in a special series of lectures on the professional aspects of military medicine.

Dr. James D. Bruce, F.A.C.P., Ann Arbor, Mich., has established the Theodore A. McGraw Memorial Scholarship, to be awarded to the outstanding junior in Wayne University College of Medicine, Detroit, in memory of the late Dr. McGraw, who was formerly President of the College when it was known as the Detroit College of Medicine and Surgery. The award is in the amount of $100.00 annually.

Dr. Victor Johnson, Associate Professor of Physiology and Dean of Students in the Division of Biological Sciences, University of Chicago, was appointed on July first Secretary of the Council on Medical Education and Hospitals of the American Medical Association.

Dr. Josiah J. Moore, F.A.C.P., Chicago, has been elected Vice President of the American Society of Clinical Pathologists.

Dr. Edward Urbane Reed, F.A.C.P., District Medical Officer of the Third Naval District, has received executive nomination for the rank of Rear Admiral.

Dr. Joseph A. Capps, F.A.C.P., Chicago, was the founder of the Joseph A. Capps Prize offered annually by the Institute of Medicine of Chicago "for the most meritorious investigation in medicine or in the specialties of medicine." The investigation may also be in the fundamental sciences, provided the work has a definite bearing on some medical problem. Graduates of Chicago medical schools who completed an internship or one year of laboratory work in 1941 or thereafter may enter competition. Manuscripts must be submitted not later than December 31 to the Institute, 86 E. Randolph Street, Chicago.

Dr. James E. Paullin, F.A.C.P., President of the American College of Physicians, Atlanta, Ga., and Dr. Tom D. Spies, F.A.C.P., of Birmingham, Ala., will appear on the program of the Eleventh Annual Assembly of the Omaha Mid-West Clinical Society, October 25–29.

Dr. Philip Work, F.A.C.P., has resigned as Professor of Neurology and Head of the Department at the University of Colorado School of Medicine, Denver, and is now on active duty in the Medical Corps of the U. S. Army as a Lieutenant Colonel.

Dr. Clough T. Burnett, F.A.C.P., has resigned from the same institution as Associate Professor of Medicine.

As a memorial to the late Dr. Walter R. Steiner, F.A.C.P., Hartford, Conn., Mr. Elisha H. Cooper, New Britain, Conn., has furnished a room adjoining Yale University's Historical Library. In this room will be housed medical memorabilia, including items of historical interest presented by Dr. Steiner during his life time.

Upwards of one and three-quarter millions of dollars will eventually go to the University of Rochester as a fund for research in Internal Medicine, as provided in the will of Mrs. Bertha H. Buswell, of Buffalo.

Dr. Cecil J. Watson, F.A.C.P., Minneapolis, Minn., has been appointed Head of the Department of Medicine and Director of the Division of Internal Medicine at the University of Minnesota Medical School.

Dr. Alphonse E. Walch, F.A.C.P., Minneapolis, Minn., has been promoted at the University to Clinical Assistant Professor of Medicine.

Colonel Edgar Erskine Hume, F.A.C.P., of the U. S. Army Medical Corps, and Dr. Tomas Cajigas, F.A.C.P., Washington, D. C., were recently awarded the medal of the Aztec Eagle for work on military medicine. Both are honorary members of the Academia Nacional de Medicina of Mexico.

According to the Journal of the American Medical Association, the Southwestern Medical Foundation School of Medicine was opened June 21 at Dallas for the registration of students. This new school originated through the Southwestern Medical Foundation, which is chartered to carry on medical education and research. This school is using temporary buildings until permanent buildings may be erected on the twenty-five acre campus, which has already been purchased. It is estimated that the entire project will have an initial fund of one million, five hundred thousand dollars to start, and that eventually ten million dollars will be expended and a fifteen million dollar endowment established. Dr. Edward H. Cary is President and Dr. Don H. Slaughter is Acting Dean of the Medical School.

Dr. Ralph K. Hollinshed, F.A.C.P., Westville, N. J., was recently installed as President of the Medical Society of New Jersey.

Dr. Walter E. Vest, F.A.C.P., Huntington, W. Va., has been reappointed by Governor Neely as a member of the Public Health Council for the term ending June 30, 1947. Since 1937 Dr. Vest has been President, and since 1933 a member of the Council.

Dr. Anthony Bassler, F.A.C.P., New York City, Dr. Clarence J. Tidmarsh, F.A.C.P., Montreal, and Dr. Harry M. Eberhard (Associate), Philadelphia, have been re-elected, respectively, President and Vice Presidents of the National Gastro-Enterological Association.

Announcement is made in a recent issue of the Journal of the Medical Association of Georgia concerning the Oglethorpe University School of Medicine, which is now seeking accreditation of the Council on Medical Education and Hospitals of the American Medical Association. The school is entering its third academic year, quarters have been built or remodeled for the departments of microscopic and gross

anatomy, biological chemistry and laboratory medicine, physiology, pharmacology, pathology and bacteriology. A Clinic has been built and organized in down-town Atlanta, to aid in teaching third year students.

Dr. Charles C. de Gravelles, F.A.C.P., New Iberia, La., was recently installed as President of the Louisiana State Medical Society.

Dr. M. D. Hargrove, F.A.C.P., Shreveport, La., was elected First Vice President.

Dr. Oscar W. Bethea, F.A.C.P., New Orleans, La., was recently installed as President of the New Orleans Graduate Medical Assembly.

The Medical School and the Woman's College of Duke University, Durham, N. C., will open on September 27 a School of Physical Therapy, the school to be conducted at Duke Hospital.

Dr. Thomas H. A. Stites, F.A.C.P., recently resigned as Medical Director of the State Tuberculosis Sanatorium at Cresson, Pa., after twenty-nine years of service to the State.

Dr. T. Dewey Davis, F.A.C.P., Richmond, Va., was recently elected President of the Richmond Tuberculosis Association, filling the unexpired term of Captain Fred W. Scott, who resigned. Dr. Davis has served as a member of the Board of Directors for many years, has been Chairman of the Medical Committee and the annual early diagnosis campaign, and also a member of the Executive Committee.

Harvard Medical School, Courses for Graduates, has announced that it will conduct a condensed one-day conference and a more extensive seminar in legal medicine. There has been a steadily increasing demand for instruction in this subject, and the facilities have been relatively limited in this country. No attempt will be made to turn out expert medico-legal specialists, but rather the aim will be to give to the average medical examiner, coroner, or other physician interested in the subject, a better general working knowledge, in order that he can better perform his day-to-day duties.

The course was initiated last year and was sufficiently popular to be repeated one month later. The course will be held at the Mallory Institute of Pathology, Boston City Hospital, Wednesday, October 6, 1943, and will be open to any registered physician, lawyer, police official, criminal investigator, senior medical student, or other person whose duties are associated with medico-legal topics.

There is no fee. An advance application is not essential. However, advance notice of intention to attend will be helpful, if addressed to Dr. William H. Watters, F.A.C.P., Department of Legal Medicine, Harvard Medical School, Boston.

There will be offered also a Seminar in Legal Medicine during the entire week of October 4–9, inclusive. This is planned particularly for medical examiners and coroners' physicians, but will be open also to any other suitable graduate of an approved medical school.

The fee will be $25.00. An application should be made on or before October 1 to Harvard Medical School, Courses for Graduates, Boston, Mass.

REPORT OF CENTRAL COMMITTEE FOR WAR–TIME GRADUATE MEDICAL MEETINGS

The Central Committee of War-Time Graduate Medical Meetings respectfully submits the following as a report of its endeavors and accomplishments since the inception of the Committee and the organization of a central office:

The Committee was officially commissioned to proceed with its plans on February 18, 1943, and a central office opened at 4200 Pine Street, Philadelphia, on March 1.

Since the beginning of the work, three meetings of the Central Committee have been held: March 14–15, in New York City; April 4, in Philadelphia; and June 26, in Philadelphia.

As a means of introduction, the Committee drew up a Statement of Organization as of March 1, which was later revised as of May 1. This Statement of Organization, together with a map showing the twenty-four regional districts into which the country had been divided and the lists of National Consultants and Regional Committee members, was widely distributed to all the key-men throughout the entire country, including the National Consultants and Regional Committee members.

On March 15, through Dr. Herman Weiskotten, then Secretary of the Council on Medical Education and Hospitals of the American Medical Association, the deans of all the medical schools of the country were contacted in the hope of enlisting their interest in and cooperation with the War-Time Graduate Medical Meetings. From fifty-five of the deans, enthusiastic replies have been received. The names of teachers from these medical schools, who will be available and eager to participate in this program, are now on file in the central office.

The Chairman of the Central Committee has met with representatives of the Rockefeller Foundation and the Commonwealth Fund and discussed the project with them.

Meetings at which the Central Committee of the War-Time Graduate Medical Meetings has already offered the facilities at its disposal include the Georgia State Medical Association Meeting which was held on May 13, 1943, at which Drs. James Means, Virgil P. Sydenstricker and William H. Evans appeared at the invitation of the Committee.

Also on May 3–5, Drs. Edwin E. Osgood and L. T. Coggeshall participated in a Refresher Course, at the invitation of the War-Time Graduate Medical Meetings, offered by the University of Alberta Hospital in Edmonton, Alberta, Canada.

The Regional Committees, to date have responded as follows:

Region No. 1—Maine, New Hampshire, Vermont, Massachusetts, and Region No. 2—Connecticut and Rhode Island, have consolidated their activities and will work in cooperation with the First Service Command and the Naval District in the New England States. Plans are nearing completion for postgraduate courses at the Newport Naval Hospital for September 14–15–16, including a one-day presentation of medical subjects, one day of surgical subjects and one day of subjects in the various fields of medicine. Approximately twenty-five speakers will be presented.

Plans are likewise being formulated for a one, two or three day program to be presented at New London in October.

This committee is also working in cooperation with the committee arranging the Clinical Congress of the 19th Clinical Congress of the Connecticut State Medical Society to be held on September 28–29.

Region No. 3—New York: Courses have already been conducted and others now being formulated. On July 23, a program covering the "Diagnosis and Treatment of Cardiac Pain" was presented at the St. Albans Naval Hospital; on July 27, a two-hour lecture in Chemotherapy was presented at the St. Albans Naval Hos-

pital; and on August 3, a lecture by Dr. Henry Meleny on "Malaria" at the Brooklyn Naval Hospital. Plans are being made for lectures in shock, burns and plasma, and the dysenteries, for some time in September.

Region No. 4—Eastern Pennsylvania, Delaware and New Jersey: The committee is extremely active and while no definite time for courses has yet been decided upon, there will be one or two presented in the early fall.

Region No. 5—Maryland, District of Columbia, Virginia and West Virginia: Interested and active committee in process of planning courses for fall.

Region No. 6—North Carolina, South Carolina: Committee active; held meeting of representatives of all military installations in this region on August 2 to decide upon needs of Medical Officers in this region.

Region No. 7—Georgia and Florida: Committee working on an excellent four week program to be presented at Service installations in Florida in early fall.

Region No. 9—Michigan: Committee proceeding in cooperation with other interested groups to offer post-graduate medical instruction to Medical Officers.

Region No. 10—Kentucky, Tennessee: Committee has planned an excellent course for week of October 3 covering burns, shock, blood derivatives and substitutes; chemotherapy; general surgery and the dysenteries.

Region No. 11—Alabama and Mississippi: Committee proceeding with basic plans best suitable for district which it covers.

Region No. 12—Louisiana: Committee exceedingly interested in program and endeavoring to offer the facilities of the War-Time Graduate Medical Meetings where such need is apparent.

Region No. 13—Texas: Plans for courses have been tentatively made.

Region No. 14—Indiana, Illinois and Wisconsin: Committee doing a superb piece of work in correlating the facilities already available with those offered by the War-Time Graduate Medical Meetings.

Region No. 16—Missouri, Kansas, Arkansas, Oklahoma: Committee proceeding with plans best suited for this district.

Region No. 17—North Dakota, South Dakota, Nebraska: Committee slowly proceeding with plans.

Region No. 18—Montana, Wyoming: Plans proceeding for courses to be offered in the autumn covering the subjects of anesthesia; shock, burns, blood derivatives; clinical psychiatry, psychosomatic medicine; cardiovascular problems; dysenteries; acute respiratory disease, physical therapy, diagnostic roentgenology.

Region No. 19—Colorado, Utah: Plans have been made for programs to be offered on September 30, and October 1, 1943, in Denver.

Region No. 20—New Mexico, Arizona: Plans being made for programs to be submitted in late fall, probably at some central point such as Albuquerque or Santa Fe.

Region No. 23—Nevada, Northern California: Interest in this program is widely apparent in this section of the country.

Region No. 24—Southern California: Rather slow progress; some difficulty in getting started with service hospitals.

No progress reports have as yet been submitted from the following regions:

> Region No. 8—Western Pennsylvania and Ohio.
> Region No. 15—Minnesota and Iowa.
> Region No. 21—Washington.
> Region No. 22—Idaho and Oregon.

The National Consultants are now compiling the names of outstanding men throughout the entire country who are willing to serve on a National Faculty. This Faculty will aid the committees in meeting the demands for teachers.

Requests have recently been received in the Central Office for speakers to appear on the program being offered by the Delhousie University for Medical Officers in the Canadian Forces during the week of October 11, and also for the annual meeting of the Saskatchewan Medical Society to be held in Reginia, Saskatchewan, Canada, on September 16, 17, and 18.

Respectfully submitted,

EDWARD L. BORTZ,
Chairman

SPECIAL NOTICE

At St. Elizabeth's Hospital, the Federal institution for the treatment of mental disorders, Washington, D. C., fine opportunities for psychiatric residencies and rotating internships are open to recent graduates of medical schools; these residencies and internships rank among the best in the United States. The Institution has 7,000 patients including members of our armed forces who are casualties of the present war. In order that these men as well as civilian patients receive adequate care and treatment, it is necessary to recruit a number of Junior Medical Officers.

The rotating internship consists of 1 year of rotating service including medicine, surgery, psychiatry, laboratory, pediatrics (affiliation), and obstetrics (affiliation). Applicants must be fourth-year students in a Class A medical school or they must have successfully completed their fourth year of study in a Class A medical school subsequent to December 31, 1935. The duties of Junior Medical Officer (Rotating Internship) are those of an interne assigned to medical, surgical, and laboratory services, and out-patient clinics.

A postgraduate internship of 1 year in psychiatry is offered to graduates of medicine who have already served an accredited rotating internship. Applicants must have successfully completed their fourth year of study in a Class A medical school subsequent to December 31, 1932, and they must have the degree of either B.M., or M.D. In addition, they must have successfully completed an accredited rotating internship of at least one year, except that applications will be accepted from persons now serving such internship. The duties of Junior Medical Officer (Psychiatric Resident) are those of a resident in the diagnosis and treatment of mental patients.

It is possible that women may be utilized in these positions. Appointments to the above positions will be made at various times during the year as vacancies arise. The positions pay $2,000 a year (plus $433 overtime pay). There are no age limits for these positions. No written test is required. Persons now using their highest skills in war work should not apply. Appointments in Federal positions are made in accordance with War Manpower Commission policies and employment stabilization plans.

The Commission would appreciate your bringing this information to the attention of qualified persons who you feel may be interested. An official announcement, amendment, and application forms may be obtained at first- or second-class post offices, Civil Service Regional Offices, and the Commission.

By direction of the Commission:

Very respectfully,

WM. C. HULL,
Executive Assistant

OBITUARIES

DR. JAMES BASSETT McELROY

Dr. James Bassett McElroy died at his home in Memphis, Tennessee, on March 24, 1943. He was 76 years old. In his death the South has lost one of its most distinguished physicians.

He graduated in medicine in 1893 from the College of Physicians and Surgeons of Baltimore, Maryland. For many years he has held a very prominent position in the University of Tennessee College of Medicine, serving as Professor of Medicine, Dean, Chairman of the Faculty, and Member of the Board of Trustees. While he was connected with the Medical School it enjoyed its greatest growth and attained its present high standing among the medical schools of the Country. Much of this progress of the School was due to Dr. McElroy's enthusiastic work in its interest.

In 1902–1903 he was Secretary of the Section on Practice of Medicine of the American Medical Association. He has been President of the Tennessee State Medical Association and of the Memphis and Shelby County Medical Society. He has been a Fellow and also a Governor of the American College of Physicians.

The accomplishments of Dr. McElroy have been many indeed and it is almost impossible to review even briefly the many characteristics of a man who crammed into one life enough work for two average lives. The young student of medicine who is seeking guidance to success in his profession would do well to emulate him. While Dr. McElroy blazed his own trail through life and would want those who come after him to do the same, nevertheless he had many traits that have been outstanding in other big men. He was a good student who was not afraid to work. He was endowed with an unusual amount of vitality. He was human, kind, very fair, methodical, conscientious and thorough.

He believed that the physician should be just a plain good doctor with a lot of real hard sense. He was a staunch friend of physicians who were trying to practice medicine the way it should be practiced and was definitely opposed to those who made little effort to keep abreast of the recent advances in modern medicine.

WILLIAM C. CHANEY, M.D., F.A.C.P.,
Governor for Tennessee

DR. WILLIAM SIMONS OVERTON

Dr. William Simons Overton (Associate), Binghamton, N. Y., was born in 1864 and died at Sag Harbor, Long Island, on May 17, 1943, of coronary thrombosis; aged, 78 years.

Dr. Overton graduated from the Long Island College Hospital of Brooklyn in 1887. In 1936 he celebrated his fiftieth year in the practice of medi-

cine. He temporarily retired and spent a year in New Mexico, then returned again to Binghamton and resumed his work. Dr. Overton also was a Pharmacist and at one time owner of the Moore-Overton Hospital. For many years he was on the staff of the Binghamton City Hospital, and he served as a member of the New York State Grievance Committee, Medical Practice Act. He was a member of the Binghamton Academy of Medicine, the New York State Medical Society and a Fellow of the American Medical Association. He was a charter member of the American Congress on Internal Medicine from 1916, and by virtue of that membership became an Associate of the American College of Physicians, which membership was maintained in good standing the balance of his life.

DR. STIRLEY CASPER DAVIS

Dr. Stirley Casper Davis was born in Owenton, Ky., October 25, 1882, graduated from the Hospital Medical College, now University of Louisville School of Medicine, Louisville, Ky., in 1906. He pursued postgraduate work in various institutions in New York, New Orleans, Philadelphia and San Francisco. He entered on a medical career that was to last thirty-seven years and make him one of the best known physicians in Arizona. The first World War interrupted his medical career briefly, for he went overseas with the Thirty-fourth Division as a Captain in the Medical Corps.

In 1920, Dr. Davis arrived at Tucson where he helped found the Thomas-Davis Clinic and he became the Chief of the Medical Staff there. For many years he was Medical Director of the Southern Pacific Sanatorium. In 1927, he became President of the Chamber of Commerce and was instrumental in securing the location of the U. S. Veterans' Hospital at Tucson.

For the past thirteen years he had been a member of the Board of Tucson School District No. 1 and served virtually half of that time as its President. During his term of office, the public school system was greatly expanded and he was responsible for many improvements in working conditions and teaching personnel.

Dr. Davis had served as President of the Pima County Medical Association and as a Director of the Tucson Sunshine Climate Club. He was also a member of the Arizona State Medical Society, a Charter Member of the American College of Chest Physicians, a Fellow of the American Medical Association and, since 1930, a Fellow of the American College of Physicians.

Dr. Davis died at Tucson, March 14, 1943, of heart disease, at the age of sixty. He is survived by his wife, Mrs. Mabel Davis, and a daughter, Mrs. Harold T. Landon.

CHARLES S. KIBLER, M.D., F.A.C.P.,
Tucson, Ariz.

DR. HAROLD W. DANA

Dr. Harold W. Dana, M.D., F.A.C.P., Brookline, Mass., died of pneumonia at his home in Brookline on May 8, 1943. He was in his sixty-sixth year.

Dr. Dana was graduated from the Harvard Medical School in 1905, served two years as house officer at the Boston City Hospital and spent a year and a half in postgraduate medical study, chiefly in Berlin and Vienna. He returned to practice internal medicine in Boston and served on the Medical Staff of the Boston City Hospital, later becoming Physician-in-Chief of the First Medical Service. He was also Associate Professor of Medicine at Tufts College Medical School.

He was certified as a specialist by the American Board of Internal Medicine. He was also a Fellow of the American College of Physicians and a member of the Massachusetts Medical Association.

Besides his medical career, Dr. Dana was a man of varied interests, being an amateur watercolor painter of note. He was a prominent member of the New England Historical Genealogical Society and had also served as President of the Massachusetts Society of Sons of the American Revolution and of the Massachusetts Society of the War of 1812.

He is survived by his widow, the former Gertrude Quinn of Dover, New Hampshire; two daughters, Mrs. Patrick Brady of Brookline, and Mrs. Henry S. Bromley, Jr., of Ardmore, Pa., and five grandchildren.

WILLIAM B. BREED, M.D., F.A.C.P.,
Governor for Massachusetts

SOME NEW APPROACHES TO THE PHYSIOLOGY OF THE THYROID *

By J. H. Means, M.D., F.A.C.P., *Boston, Massachusetts*

It is presumptuous, perhaps, for me, a clinician, to undertake to discuss a problem in physiology. My excuse is, of course, that knowledge of the function of organs is gained not only by planned experiment, but also by taking advantage of the experiments which nature presents in the form of disease. Not infrequently nature's method has provided the earlier and sometimes the more important information. My own approach to the thyroid has been, at least of late years, more in the clinic than in the laboratory, but my colleagues have indulged in planned experiment by newer methods as well, and my purpose is to correlate those various experiences and attempt to derive a picture, however fragmentary, of thyroid function as a whole.

According to current belief, the thyroid gland has the function of manufacturing, storing and delivering to the body, as needed, its own one peculiar hormone, which I shall refer to henceforth as thyroid hormone. Whether this is an altogether correct conception, as I shall indicate later, in view of recent knowledge is open to question.

In our consideration of thyroid function as a whole we must include the manner in which the hormone acts upon its end-organs, what finally becomes of it, and how its rate of secretion is regulated. The term "end-organ" implies an analogy with the nervous system, and, indeed, such an analogy is useful. On the one hand, we have the nerve cell or neurone, with its axis cylinder conveying a stimulus neurally to an end-organ; on the other, the endocrine cell conveying a stimulus humorally, by means of its hormone, also to an end-organ. The nervous system and the endocrine system constitute two great integrating mechanisms of the body, and they are themselves coördinated one with the other.

In the control of thyroid function the most conspicuous endocrine factor is the anterior pituitary which secretes a hormone which specifically stimulates the thyroid to make its own hormone. This has been variously called the thyreoactivator, the thyrotropic or thyroid stimulating hormone (TSH we may call it, analogous to FSH, the ovarian follicle stimulating hormone). There is also fast growing evidence that the thyroid hormone depresses the pituitary with respect to TSH secretion and thus the two glands come into hormonic balance and form a system of automatic control. To this balance, Salter[1] has given the appropriate name of "pituitary-thyroid axis" (figure 1). There are other similar axes in the endocrine system, for example, the pituitary-gonadal. So fundamental is this glandular interrelationship that I may now restate my objective as a consideration of the pituitary-thyroid axis and influences which impinge on it. The latter will include such agents as iodine, or lack of iodine, vitamins, cyanides, cyanates, sulfa compounds and the unknown agents which cause disease. The physiology which I shall lay before you will be morbid as well as normal.

Let us now review the approaches to this objective. The earliest approaches to thyroid physiology unquestionably emerged from the clinic. Because the primary action of the thyroid hormone is the calorigenic, the measurement of basal metabolic rate is the time honored and most extensively used measuring stick of thyroid function. It is a measurement of the effect of the hormone upon its end-organs. How much does the hormone increase the rate of oxidation of tissue cells? The determination of the rate of respiratory metabolism goes back to Lavoisier who, you will recall, had his head severed by the guillotine in the French Revolution, his prosecutor saying, "La République n'a pas besoin de savants." The application of such measurements to the function of the thyroid began in Germany in the 1890's when Magnus-Levy[2] measured the respiratory metabolism of patients with hyper- and hypothyroidism, and of normal persons after thyroid feeding. Since that time, particularly as a result of the impetus given it by the pioneer work in clinical calorimetry of Du Bois in this country, the determination of the basal metabolic rate has become a well nigh universal clinical procedure.

Among other now well explored approaches to thyroid physiology may be mentioned the attempts to stimulate the gland through nervous pathways[3, 4] and the observation microscopically of cyclic events in the thyroid cells and follicles.[5, 6, 7, 8, 9] The discovery by Baumann,[10] in 1896, that iodine is a normal constituent of the thyroid blazed the pathway for the biochemical approach. Milestones along this route are Kendall's[11] isolation, in 1915, of the iodine-containing amino-acid, thyroxine, and his demonstration that it exerted the physiologic properties of whole thyroid, and Harington's and Barger's[12] synthesis of this substance in 1927. Yet another approach, contemporaneous with these, is the observation of the effect of thyroid hormone upon the metamorphosis of amphibians, exploited first by Gudernatsch[13] and later by Uhlenhuth.[14]

In considering newer approaches and what has been learned by them, we may well start with those studies which have been designed to discover what actually constitutes the thyroid hormone.

You are aware that the hormones of the anterior pituitary are proteins and that those of the adrenal cortex and gonads are sterols. In the case of the thyroid, at least, it can be said that the amino-acid thyroxine, or tetraiodo-thyronine, given in chemically pure form parenterally in suitable dosage, will totally relieve a state of complete athyreosis. But other substances, albeit to less degree, exhibit this power. For example, if two atoms of iodine are withdrawn from the thyroxine molecule (the 3'.5' iodine atoms of the outer ring) a compound known as diiodothyronine results. This exhibits thy-roxine-like activity, but in degree only 4 per cent of that of thyroxine. Finally, diiodotyrosine, which possesses two iodine and but one phenyl group, exhibits very slight calorigenic action, but will not relieve human myxedema. It is well established that for thyroxine-like activity, that is to say, power to relieve athyreosis, the presence of iodine in the hormone molecule is indis-pensable. Moreover, as Salter [1] has pointed out, the high degree of activity of thyroxine is connected also with its diphenyl-ether-alanine structure.

The thyroid hormone is stored in the follicle of the thyroid gland in protein combination—the so-called iodothyroglobulin. This protein can be broken down by alkaline hydrolysis or, as Harington and Salter [15] have shown, by proteolytic digestion, into its component amino-acids. When this is done it is found that all of its iodine is divided between the two amino-acids thyroxine and diiodotyrosine.

When whole thyroid gland is fed to an athyreotic human being, it exerts a physiological activity which, as Lerman and Salter [16] have shown, is pro-portional to its total organic iodine content. This is rather remarkable, be-cause, as said earlier, diiodotyrosine has but a very slight physiological activity. One would expect that whole thyroid or purified thyroglobulin would have a physiological effect proportional to its thyroxine iodine alone, but such is not the case. The diiodotyrosine iodine also is reflected in the total physiological activity. One is forced to conclude, from this seeming paradox, that in the body diiodotyrosine can be converted into thyroxine by some form of enzyme action. Such action probably cannot take place, however, unless to start with the diiodotyrosine is in some form of peptide or peptone combination. The thyroid gland is not essential to this con-version because it takes place in the thyroidless person.

Thus emerges the broader question of whether the thyroid gland is essen-tial to thyroid-like function or merely a luxury with respect to it. Or what are the elements in extrathyroidal elaboration of thyroid hormone?

Salter's approach to this problem has been along the line of in vitro synthesis of physiologically active thyroid-like materials. Harington and Salter, having shown that by peptic digestion natural thyroglobulin can be split into active thyroxine-peptone, Salter and Pearson [17] proceeded, by suitably readjusting concentrations, solubilities and temperatures, to reverse the proc-

ess and bring about an enzymic (peptic) synthesis of an artificial protein, having thyroid-like activity, from inactive diiodotyrosine peptone. But even enzymic synthesis is not essential to the in vitro and extrathyroidal production of physiological activity, because subsequently Salter and Lerman [18] found that if indifferent protein, serum protein for example, is simply treated with compound solution of iodine in an alkaline medium without any enzymic assistance, an iodinated protein is formed which when administered in suitable dosage will completely relieve human myxedema. This is a remarkable finding and raises the further question of which came first, the hormone or the endocrine? Seemingly the endocrine is not necessary, because if our dietaries constantly contained sufficient iodinated protein we would not have need of thyroid glands. No doubt species lower in the animal scale than we, and not possessing thyroid glands, get on in this manner. We might iodinate our beef steaks before cooking them, provided we could get the beef steaks, and get on thyroidless very comfortably.

The physiological activity of such artificially iodinated protein, however, is low in terms of its iodine content as compared with that of natural iodothyroglobulin, the ratio being 1 : 4,000. This is probably because its iodine is in the form of compounds having low physiological activity and not convertible in vivo into thyroxine by the thyroidless individual.

From all this it would seem that the most plausible theory of the relation of the thyroid gland to thyroid hormone production is that the first steps in the elaboration of physiologically active material are extrathyroidal, but that the gland, by converting enzymically compounds of low activity into highly active thyroxine, serves to increase hormonic efficiency many hundred fold. As to which came first, the gland or the hormone, I think we can safely say the hormone, but in a form of low potency. The evolution of the gland, like the evolution of the cerebral cortex with respect to sensory and motor activity, has raised the whole function to one of high powered efficiency. This same line of reasoning probably applies to other endocrine glands also.*

As indicated earlier, the thyroid gland is not only a factory, but a storage warehouse as well. A consideration of the conditions under which it makes, stores or delivers its hormone, however, we may postpone until we have had opportunity to glance at the other end of the pituitary-thyroid axis. At the moment let us see what approach we have to the conveyance of the hormone to its end-organ, and how it acts upon it.

Years ago that great figure in thyroidology, the late Dr. Henry S. Plummer,[20] defined thyroxine as "an agent hastening the rate of formation of a quantum of potential energy available for transformation on excitation of the cell." He further said: "Thyroxin is active directly or indirectly in the

---

* Since the preparation of this manuscript the paper of Reineke and Turner [19] has appeared, in which it is reported that artificial iodinated proteins can be prepared, having several times the physiologic activity and thyroxine content of natural whole thyroid gland.

cells throughout the tissues of the body." I am not physicist enough to understand the quantum theory, in fact, I am not a physicist at all, and I am not certain that Dr. Plummer was; none the less, I think we can easily see what he was driving at, and in the main agree with him. Certainly when the thyroid hormone, be it thyroxine or other, impinges on the cell, its end-organ, energy transformation in the cell is accelerated. Or if we prefer, the vital flame is caused to burn more brightly.

The approach to the action of the thyroid hormone on its end-organs, which depends upon the measurement of gas exchange of the entire organism, that is to say the measurement of basal metabolic rate, is an old one. A newer one is that of determining the effect on the gaseous metabolism of isolated tissues in vitro by means of the Barcroft-Warburg apparatus. By this latter method several approaches are available. One may, for example, give hormones to animals and then sacrifice and determine the metabolism of isolated tissues, or one may excise tissues and expose them to substrates to which hormones have been added.

By the former method it has been found that the oxygen consumption of isolated tissues (QO_2 it is generally called) of animals made thyrotoxic by thyroid administration is higher than that of untreated animals, except thyroid tissue, which is lower.[21, 22, 23]

Salter and Craige [24] have used the action of patients' plasma on the QO_2 of mouse liver as a test of thyroid function. The plasma of thyrotoxic patients raised, that of myxedematous ones lowered the QO_2 relative to the normal control. The authors point out that the basal metabolic rate of the subject is vicariously reflected in the metabolic rate (QO_2) of the liver tissue exposed to his plasma. They, therefore, used the term VMR—vicarious metabolic rate—and found a very good agreement between it and the BMR.

The approach to hormone action in isolated tissue by adding hormone directly to the substrate bathing it is well exemplified by the work of Canzanelli and Rapport.[25] These investigators, in one series of experiments, determined the effect of thyroglobulin and derivatives of it on the QO_2 of guinea-pig liver and of rat liver. Pure thyroxine had no effect on the QO_2 of either tissue. Thyroglobulin, on the other hand, markedly increased the QO_2 of each. Diiodothyronine had a variable but on the whole negligible effect and diiodotyrosine had no effect on guinea-pig liver and consistently depressed the QO_2 of rat liver. From these observations the authors concluded that thyroxine is not the thyroid hormone and that the hormone is either thyroglobulin or an integral part of it.

If thyroglobulin is to be looked upon as the hormone, however, one would expect to find it in the circulating blood en route from thyroid to end-organ. This, however, has not been done. On the contrary, its absence from the blood stream has been established by Lerman,[26] who produced a thyroglobulin antiserum by injecting human thyroglobulin into rabbits "which was able to detect by precipitin reaction minute amounts of thyroglobulin in solution, namely 0.08 to 0.15 mg. per 100 c.c." By means of this reaction Lerman

could find no detectable thyroglobulin in the blood of normal persons or of myxedematous persons or of thyrotoxic persons either before or after iodinization. The only time Lerman could detect appreciable amounts of thyroglobulin in the blood was when he obtained samples from the thyroid vein toward the end of an operation during which the surgeon had been handling the thyroid. Evidently at operation some intact thyroglobulin is milked into the blood stream, but Lerman was able to show that after operation it disappears very rapidly. Either it is destroyed or fixed by the tissues. From this work of Lerman's together with that of Canzanelli and Rapport, we may draw the conclusion that thyroid hormone travels from the thyroid to its end-organs in a form lower than the protein level, and that it acts upon its end-organ in a form of higher level than that of the amino-acids. It may both travel and act in the form of a polypeptide or peptone. Certainly there is thyroxine iodine in the blood, and if not in the form of thyroglobulin, it is probably in the form of split products thereof.

The blood can be studied as to its thyroid hormone concentration by fractioning its total organically-bound iodine. This approach has been used by many investigators, often, because of technical difficulties, with conflicting results. Now, however, with improved methods dependable figures can be got, and Bassett, Coons and Salter [27] have shown that the protein-bound iodine of the blood can be used as a dependable index of circulating thyroid hormone. In studying patients with either hyper- or hypothyroidism there was an even closer correlation between this factor and the estimate of thyroid function based on symptoms than between the latter and basal metabolic rate.

Canzanelli, Guild and Rapport [28] have further shown, in a more recent study, that thyroglobulin directly applied will also raise the QO_2 of guinea-pig testis, kidney and heart muscle. There appeared, however, to be a ceiling beyond which increasing concentration of hormone had no additional effect.

In contrast to this Galli-Mainini,[29] of Buenos Aires, who spent the years 1940 and 1941 working in our laboratory, obtained evidence that thyroglobulin depresses the QO_2 of guinea-pig thyroid tissue. If this result is correct, and I may say that it remains to be confirmed—although it is in agreement with the in vivo work which I have cited—it signifies that the thyroid hormone has an effect upon the cells which make it opposite to that upon indifferent cells of the body. Moreover, there is rapidly increasing evidence that the thyroid hormone depresses the anterior pituitary with respect to the production of thyroid stimulating hormone. Thus it may well be that within the pituitary-thyroid axis we have two self-regulating or automatic apparatuses, in each of which rising thyroid hormone production leads, through elevated thyroid hormone blood level, to decreased thyroid hormone production (figure 2). In one case the hook-up is thyroid to pituitary to thyroid, in the other thyroid to thyroid. It is to be doubted that either the thyroid cell or the pituitary cell is exempt from the general thyroid hormone action of stimulation, but in the case of these two tissues there may be in

addition a specialized action of inhibition which more than cancels that of stimulation.

When we approach either the elaboration, or better perhaps the finishing of a hormone by an endocrine, or the action of a hormone on its end-organ, we get nowadays at once into enzyme chemistry, for these processes are certainly enzymic, and unfortunately I am no more enzyme chemist than physicist.

However, we all perhaps now know that oxidation in a living cell, in contrast to that in a Bunsen burner, is a complicated series of reactions involving the tossing about of hydrogen and oxygen atoms from molecule to molecule under the influence of enzymes with a resulting oxidation at body temperature, instead of a simple and violent union of oxygen and hydrogen with liberation of great heat and without benefit of enzymes or catalysts, as is the case in the Bunsen burner. On this oxidative enzyme system of the cell the thyroid hormone somewhere impinges to cause acceleration.

Of course, there are other actions of thyroid hormone than that of increasing the rate of metabolism of the cell or the whole organism, but these may be looked upon as associated or by-effects of the fundamental oxidative action. Among these may be mentioned its action on growth, metamorphosis and the differentiation of tissue (all of which are accelerated), and also upon the distribution and exchange of water, salts and colloids of the body, upon hepatic glycogen stores (which are depleted under an excess of the hormone), upon the circulation (which is accelerated), upon the nervous system (which is rendered more irritable) and others.

Let us now go to the other end of the pituitary-thyroid axis and consider TSH and its action. Of its structure, beyond that it is protein, we know but little. However, it is possible to extract protein material from the anterior lobe in such a way that the other characteristic actions, such as gonadotropic, adrenotropic and growth promoting, are largely eliminated and only the thyroid stimulating remains. One can, in other words, obtain a fairly pure preparation of TSH. With such preparations many interesting experiments can be performed.

For example, material of this kind, when administered parenterally (being protein it is digested when given by mouth and rendered inert), will cause the thyroid epithelium to increase in height and show cytologic evidence of increased secretory activity. It also will cause an increase in QO_2 of thyroid tissue either in vivo or in vitro. It will bring about discharge of stored colloid from the follicles and, in the whole organism, elevation of metabolic rate, and all that goes with a greater output of thyroid hormone. At least it will call forth such responses for a time, but ultimately a refractory stage is reached in which the organism may swing to a hypothyroid level despite the continued administration of TSH. Such development of refractivity could be due either to the exhaustion of the thyroid or to the development of some type of antagonist to TSH.

It is obvious that the thyroid is the chief end-organ of the pituitary thyrotropic hormone. As one of my colleagues has put it, TSH plays the rôle of thyroid hormone to the thyroid gland. The question arises, however, are there other (non-thyroid) end-organs directly affected by TSH? Probably there are; however, but little is known of them. In the development of exophthalmos, either experimental or spontaneous, TSH may be a factor. In animals, exophthalmos has been observed to follow the administration of TSH, and this effect is more pronounced in thyroidectomized than in intact animals. Also, as I shall indicate a little later, in certain cases of
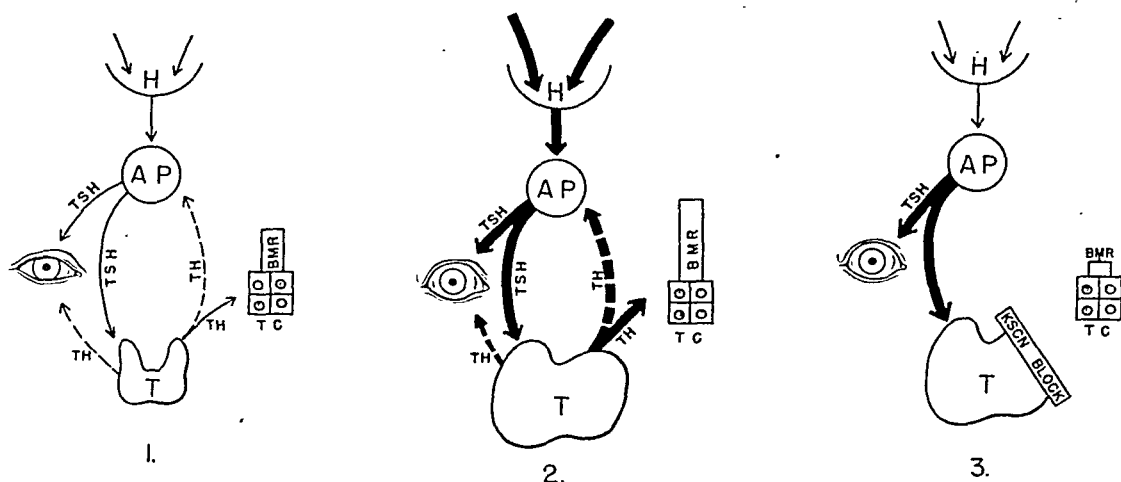
FIG. 1. The pituitary-thyroid axis.

(1) *In the normal individual.* Nervous influences impinge on the hypothalamus, H, which in turn stimulates the anterior pituitary, AP. The anterior pituitary stimulates the thyroid, T, humorally, by means of its hormone, TSH. The thyroid thus stimulated produces its hormone, TH, which stimulates tissue cells, TC, to increase their oxidative processes, BMR. Also TH inhibits AP, indicated by broken line, thus comes about the balance. A secondary effect is indicated upon the eye. TSH promotes exophthalmos, TH inhibits it.

(2) *In Graves' disease.* Hypothalamic stimulation of AP may be increased as shown by heavier arrows. Increased TSH causes hyperfunction and hyperplasia of T. Increased TH raises the BMR of TC, but at the same time there should be some inhibition of AP. TSH, it is believed, also promotes exophthalmos, which even increased TH cannot altogether offset. This interpretation is admittedly hypothetical. The primary event could be in hypersensitivity of thyroid to TSH or hypersensitivity of tissue to TH, or hyposensitivity of AP to inhibition by TH. More data are needed to settle these points. The present interpretation is offered as a first approximation.

(3) *Under the influence of cyanate.* The primary event here seems to be the imposition of a block which prevents the completion of TH. This absence of TH causes stimulation of AP with increased production of TSH, which causes hyperplasia of T, but because of the block, no production of TH. The BMR of TC accordingly falls and the unopposed TSH causes exophthalmos. (With apologies to F. Albright.)

Graves' disease in human beings in which thyrotoxicosis is minimal or absent and the eye involvement maximal, an excess of TSH can be demonstrated in the urine. How TSH is related to the swelling of orbital tissues, which causes exophthalmos, is quite obscure, but that it has something to do with it and that this action is independent of the thyroid, seems most likely. In other words, TSH, or some derivative of it must have other end-organs than thyroid tissue.

The action of TSH on thyroid cells has been studied by Rawson [30] and his co-workers by means of tissue culture technic. Explants of rabbit thyroid were bathed with fluids containing known amounts of TSH. After a suitable period of incubation, they were withdrawn and subjected to bioassay for thyrotropic activity. The remarkable finding was that all such activity had disappeared. The thyroid cells had inactivated their stimulator. The effect of other tissue explants on TSH was also studied. Lymph node and thymic tissue caused partial inactivation; adrenal, kidney, ovary, pancreas, parathyroid, testis, spleen and stomach mucosa caused none.

Subsequently, Rawson [31] was able to show that the inactivated TSH could be partially reactivated by heating, in the presence of mild reducing agents, the fluid which had been exposed to the action of thyroid.

Thus it appears that when thyroid is stimulated by TSH the hormone is inactivated, but it is not destroyed. Its activity can be restored by simple reduction.

In 1936, Hertz and Oastler [32] by bioassay, had found thyrotropic activity in the urine of certain patients with myxedema, but had failed to find it in the urine of either normal or thyrotoxic persons. Rawson,[31] however, repeating this work has been able to show thyrotropic activity in all these urines after heating. Evidently TSH is present in all, but in the normals and thyrotoxics chiefly in the inactivated form.

Rawson [33] has also made explants of tissue from human thyroids, both normal and abnormal, removed at operation. The normal thyroid tissue was obtained at operation upon parathyroid lesions. The surgeon obligingly snipped off a bit of thyroid tissue also for explantation. Exposure of known quantities of TSH in solution to these various explants disclosed that the glands taken from persons in a thyrotoxic stage of Graves' disease had a greater power to inactivate TSH than normal glands. Thyroid tissue from persons with non-toxic nodular goiter had no TSH inactivating power at all. It appears that in the toxic phase of Graves' disease the thyroid gland is under increased stimulation by TSH and that in this process an increased amount of TSH is inactivated and excreted in the inactivated form in the urine, from whence it can be recovered by artificial reactivation.

One would like to learn the precise nature of the reaction between TSH and its end-organ, the thyroid cell. Is it similar to that of the thyroid hormone on its end-organ cell? Some light is being thrown on this question by work now in progress in our laboratory by Graham and Rawson. It has been found by these workers that the inactivation and reactivation of TSH can be carried out entirely in the test tube, without any interposition of thyroid cells, by the use of mild oxidizing agents for inactivation and mild reducing agents for reactivation. This suggests that when TSH encounters thyroid tissue it becomes inactivated by an enzymic oxidation reaction. Inactivation of the hormone seems to be an accompaniment of its stimulating action on its end-organ.

The next new approach to thyroid physiology which I should like to discuss with you is that which employs radioactive iodine as an indicator. As far as I am aware, the first paper on the use of tagged iodine as a means of studying thyroid function is that of Hertz, Roberts and Evans,[34] which appeared in 1938, a publication from the Thyroid Clinic of the Massachusetts General Hospital and the Physics Department of the Massachusetts Institute of Technology. The idea of such a method originated with Hertz after he had listened to President Carl T. Compton of the Massachusetts Institute of Technology speak at the Harvard Medical School on what aid physics can render to biology and medicine. Similar work was started shortly afterward by Hamilton and Soley [35] in San Francisco, and by Leblond [36, 37] and his co-workers, in Paris and later in Rochester, New York.

The principle involved is that the thyroid has a specific avidity for iodine, obviously because iodine is an indispensable ingredient of its hormone, and that, if iodine can be labeled, a new method of studying thyroid physiology is available.

Tracer studies by means of tagged atoms are now being employed in a very wide range of physiologic and biologic problems. Usually the tagging is accomplished by making an atom temporarily radioactive by bombardment of a suitable target with neutron or deuteron beams. Another method of tagging is by using stable isotopes of the substances in question, such as deuterium or heavy water. The method of radioactive labeling has the great advantage over older chemical methods that the course of an atom, or molecule into which a radioactive atom has been incorporated, can be followed through the body in vivo and its disposition in tissues, or even cells, can be determined after excision with far greater precision than any chemical method could achieve. Hamilton, Soley and Eichorn,[38] for example, allowed slices of thyroid which had collected radioactive iodine to take their own photomicrographs. Examination of such pictures betrayed the exact location of iodine in the tissue even down to the cytologic level.

In their earlier work, Hertz and Roberts [34] used a short-lived (26 minute half period) isotope of iodine, derived from a radium-beryllium source. With this material, experiments of short duration only could be accomplished, and only animals studied, because excision of tissue was necessary for detection of iodine distribution. Much was learned, however, even thus and very soon other isotopes of iodine with half periods of 12.5 hours, eight days and 13 days became available. These were produced by bombardment with the beam from the cyclotron.

The original purpose of the animal studies was to discover the laws governing the collection of iodine by normal and hyperplastic thyroid glands and to establish the normal and pathologic behavior of the thyroid toward iodine under various circumstances. There was the hope, too, that such studies might yield information which would later permit the use of radioactive iodine for therapeutic purposes. This hope has now been realized.

In experiments on rabbits receiving iodine intravenously, it was found

that the percentage collection from any given dose reached a maximum within ten minutes, and that this was not exceeded for periods of collection as long as several days. The normal thyroid was found to collect up to 80 times the quantity to be expected from uniform diffusion into the general tissues of the body. In thyroids made hyperplastic by giving the animal TSH, cyanates or placing it on a diet high in cabbage, it was found that the relative concentration of iodine in the gland might reach several hundredfold. Another finding of interest was that the percentage uptake of iodine by the thyroid increases as the size of the dose decreases. Relatively more of a small dose is collected than of a large one; but, if the smaller dose is adequate, the total amount collected from it will be the same as that collected from larger doses. There appears to be a ceiling for iodine collection by the thyroid gland. Thus the thyroid very rapidly takes up iodine from even very small doses to the point of saturation and after that lets it pass on to the organism as a whole. The effect of a previous dose of ordinary iodine on the subsequent collection of a labeled one of standard size was found to be a reduction which was related to the size of the pretreatment dose. That is to say, if the gland had previously been well filled with iodine, its collection of a subsequent labeled dose was consequently diminished. This is the result which would be expected from what had previously been learned of the thyroid's iodine-collecting behavior. This information was secured by the method of multiple labeling, that is to say, using isotopes of different half lives which could be distinguished one from another in the body. This principle of multiple labeling, incidentally, affords an important new approach to thyroid and other physiology.

In further extension of their work, Hertz and Roberts [39] compared the effect of TSH administration in rabbits upon uptake of radioactive iodine, thyroid cell height, relative size of the thyroid and basal metabolic rate. It was found that cell height, relative thyroid size and basal metabolic rate vary essentially in parallel under the influence of TSH. The collection of radioactive iodine, given in a standard dose, follows these factors up to the point at which the ceiling for such collection is reached. Beyond that it cannot increase.

The effect of pretreatment with iodine causes the final values for all factors reached after TSH to be lower than if no such pretreatment with iodine had been given. Hertz and Roberts concluded that the effect of giving TSH is initial stimulation of the thyroid cells to collect iodine followed by involution (colloid storage in the follicles), if iodine treatment is given. However, if one continues TSH administration without iodine, exhaustion of the thyroid ultimately takes place, that is to say, loss of its capacity to collect iodine.

When sufficiently active preparations were available, Hertz and Roberts [40, 41] extended their studies to human beings. By means of Geiger counters placed over the thyroid it was possible to follow the deposition of labeled iodine in the gland and its subsequent departure. Blood levels of

tracer iodine and its elimination in the urine were also followed. In the case of 22 thyrotoxic patients, whose goiters were removed by the surgeon, it was possible, with the collaboration of Salter, to determine the chemical distribution of labeled iodine as between thyroxine-like and non-thyroxine-like fraction of the total organic iodine content.

As in the case of animals, it was found that the hyperplastic thyroid (in this case that of Graves' disease) collects more iodine than the gland of the healthy person. Also, as in animals, the relative uptake is largest at low dosage levels. The hyperplastic thyroid in the thyrotoxic phase of Graves' disease may collect initially 80 per cent or more of a dose of 2 mg. The rapidity of collection of iodine by the thyroids of either man or animal is such as to support the view that the time required is merely that taken by the iodine to reach the thyroid. Having been collected, radioactive iodine is observed to disappear slowly, in the case of the hyperplastic gland more rapidly than in the case of the normal one. Analysis of the thyroid after operation showed that the radioactive iodine was increasingly in the form of the thyroxine-like fraction the longer the time between administration and analysis. No chemical analyses could be made on normal human thyroids, because we have not yet felt justified in removing them. Total thyroidectomy for heart disease might afford an opportunity, but that procedure has largely fallen into disuse.

We may perhaps summarize the tracer studies by saying that in both man and animal iodine is taken up by the thyroid to its saturation point as fast as it reaches the gland. The ceiling is greater in the case of hyperplastic than in normal glands. In the thyroid the iodine is used, probably, partly to convert the tyrosine of thyroid protein into diiodotyrosine, and partly to convert diiodothyronine into thyroxine. The actual disposition will depend on the preëxisting state of iodination of the amino-acids already in the gland. When more iodine is supplied to the thyroid than it can utilize, it is allowed to pass by in the blood stream and in due course is excreted. There is no evidence of a storage depot of importance for iodine in the body other than the thyroid.

The release of iodine from the thyroid, other than that which merely passes through it having been refused collection, must be in whatever form the thyroid hormone is delivered to the blood. I have previously indicated that the evidence points to this being somewhere between the amino-acid and protein levels.

When, in Graves' disease as in animal experiments, a dose of ordinary iodine was given previous to the labeled, the collection of the latter was consequently decreased. This is perhaps what would be expected.

The iodine requirement of hyperplastic glands is undoubtedly greater than of normal glands because they are making, or trying to make, more of the iodine-containing hormone. In the uniodinized case of Graves' disease the thyroid is poor both in total quantity of stored protein and also in the degree of iodination of its protein. The work of Hertz, Roberts and

Salter [40] shows that such a gland cannot become saturated with iodine by accumulating small amounts, but tends rather to make it into hormone and release it.

Let us now consider the pituitary-thyroid axis from the point of view of agents or influences which may affect it (figure 1). TH and TSH are inherent parts of the axis itself. Iodine is a necessary ingredient of the hormone, and supplying it when it is deficient is bound to have important repercussions. Of other agents I wish to discuss briefly cyanides, cyanates, and sulfa compounds, and of influences, the influence of disease.

It has been known for some years, chiefly as a result of the work of Hunt,[42] Chesney [43] and his collaborators, and Marine [44] and his, that cyanides alter thyroid function, in fact, that they may produce goiter and at the same time cause hypothyroidism.

A little over a year ago, a patient [45] appeared in our clinic who had been taking potassium thiocyanate for about a year as treatment for essential hypertension. Recently he had rapidly developed a goiter, which on physical examination proved to be so hard as to suggest malignancy. At the same time he began to complain of symptoms quite characteristic of hypothyroidism, and still further to confuse the picture, we observed that he had slight exophthalmos. We succeeded in obtaining a biopsy of the thyroid, and it turned out to be wildly hyperplastic. The thought at once was that the cyanate had caused this paradoxical picture, namely, hyperplastic goiter with hypothyroidism, and it was decided, therefore, to note the effect of omitting it. Upon omission, the goiter rapidly disappeared and the basal metabolic rate rose from minus 18 to plus 5, the blood protein-bound iodine from 2.1 to 5.0 gammas. A similar case was presently reported by Kobacker,[46] and we were told of a third by Blumgart.

Evidently cyanides, and seemingly cyanates, or sulphocyanates as well, may cause a situation in which the thyroid is thwarted in its attempt to supply its end-organs adequately with its hormone. Two possibilities emerge: first, that the end-organs' responsiveness is depressed by the agent with the result that the thyroid undergoes hyperplasia and pours out an excess of its hormone; and second, that the agent acts upon the thyroid itself and in some way prevents the completion of hormone manufacture. That cyanides suppress tissue oxidation lends weight to the end-organ theory, but the weight of more recent evidence favors the view that the action is on the factory which turns out the hormone. Lerman, for example, gave to a patient with myxedema who was being maintained in a steady state at BMR minus 10 to minus 15 by a daily ration of thyroid gr. 1½ gr., 15 a day of potassium sulphocyanate for six weeks, in the meanwhile thyroid being continued as before. No fall in basal metabolic rate occurred, which indicated that potassium sulphocyanate does not oppose the action of thyroid hormone upon its end-organ. Cyanate goiter patients, on the other hand, taken off the drug, show a drop in basal metabolic rate when it is resumed. Also blood

iodine falls even ahead of basal metabolic rate. The inference is that the action is upon their thyroids. The myxedema patient having no thyroid capable of function failed to respond.

It is to be noted further that iodine will prevent cyanide goiter, and as it has been known since the early work of Marine that iodine want will cause thyroid hyperplasia, the effect of cyanide might be interpreted as being to raise the thyroid's iodine requirement, or, if you prefer, to lower the point at which iodine want becomes manifest in cytological and functional expression.

Marine has claimed that the thyroid made hyperplastic from any cause may be made to involute by giving an excess of iodine, but quite recently it has been shown by the MacKenzies,[47, 48] in Baltimore, and Astwood,[49, 50] in Boston, that the sulphonamide drugs will cause a type of hyperplastic goiter accompanied by hypothyroidism, preventable by giving thyroid, but not preventable by giving iodine. Astwood has found that feeding rats on a large series of compounds containing the thiourea nucleus and also certain aniline derivatives will do the same. The use of such substances, together with that of cyanides and cyanates, constitutes, I feel certain, an important new approach to thyroid physiology.

If we liken the elaboration of thyroid hormone by the thyroid to that of "flivvers" in the assembly line at River Rouge, then it appears that these various agents, like cyanides, cyanates, sulfa drugs, thioureas, and so forth, impinge at various points to throw the line out of gear and frustrate the completion of a perfect hormone. Because the effects of cyanides and cyanates are preventable by iodine, whereas those of sulfa drugs and so forth are not, it is to be presumed that they block the assembly line at different points.

Finally the study of naturally occurring disease is a fruitful approach to thyroid physiology. I have recently discussed the nature of Graves' disease with the Vanderbilt Chapter of Alpha Omega Alpha.[51] The chief point I should like to make about it at present is that here is another influence which impinges on the pituitary-thyroid axis to upset it, or force it into a new and pathological type of equilibrium.

What the morbid influence is which causes Graves' disease, no one knows with certainty. At present it seems likely that nervous impulses which strike it via the hypothalamus-pituitary route are important causative factors. The consideration of immediate interest is that the thyroid becomes hyperplastic and presumably turns out an excess of thyroid hormone, so much so in fact that it becomes drained of its reserve supply of hormone stored in its follicles as iodothyroglobulin. Some writers have claimed that the situation is one of thyroid failure, but the only sense in which the thyroid fails, so far as I can see, is that it fails to get iodine enough to iodinate all the hormone it would like to make under the influence of morbid stimulation.

When iodine is given in Graves' disease, as you all well know, some very dramatic events take place. The hyperthyroidism rapidly declines and the

thyroid undergoes involution.   If the hyperplastic thyroid of Graves' disease were like that of cyanate goiter, one would expect, under the influence of iodine, that more hormone would be produced and the basal metabolic rate would increase.   But such is not the case.   Seemingly in Graves' disease the action of iodine is complex.   Iodination of thyroid protein is undoubtedly accelerated, but at the same time the high concentration of iodine in the blood throws the reaction in the direction of colloid storage in the follicles rather than delivery of more hormone to the blood.   The gland fills up with well iodinated colloid, but, if administration of iodine is continued, finally the saturation point is reached and then at last an excess of hormone spills over into the blood stream.   Iodine in a sense imposes, as do cyanide, cyanate or sulfa drugs, an impediment to the delivery of thyroid hormone, but at a quite different point.   Instead of obstructing the assembly line, it may push the finished product into the warehouse instead of permitting free distribution to the body—economic or biologic.

I shall now recapitulate and at the same time attempt a synthesis.

We can imagine perhaps a remote ancestor emerging from the primordial ooze and discovering, rhetorically of course, that his protoplasm would
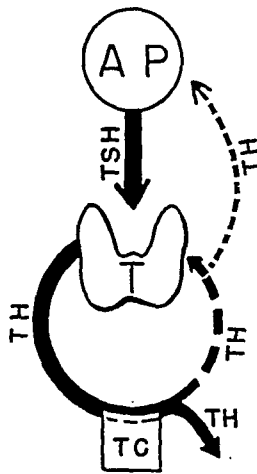
FIG. 2.   Galli-Mainini's conception of the pituitary-thyroid axis.

The anterior pituitary, AP, stimulates the thyroid, T, by means of its hormone, TSH. T then makes its hormone, TH, part of which decays in the act of stimulating tissue cells, TC. Another portion of TH remains in the blood stream and inhibits T directly, also AP.   Thus the double regulation comes about.

transform energy more rapidly if he iodinated some protein and used it as a respiratory catalyst.   There being plenty of iodine in the sea water, this offered no great difficulty.   The iodination of protein took place as a simple chemical reaction.   The iodine was attached probably as diiodotyrosine or diiodothyronine.

After the passage of some aeons the vertebrate stage was reached and then more efficient systems were evolved. Enzymes—iodases—appeared and promoted more rapid transformations. A finishing off factory in which a high powered respiratory catalyst, thyroid hormone, could be fabricated from the lower iodinated forms was obtained by converting a digestive gland into an endocrine. This involved the loss of its duct. It became, in fact, ductless. The cells of this so-called thyroid gland learned to collect iodine from the blood stream with great avidity and rapidly, through the mediation of enzymes to incorporate it into the thyroglobulin molecule which could then be either stored in the follicles or split up and delivered to the blood stream.

Regulatory devices came into being (figure 2). Probably they are but manifestations of mass action. A low concentration of thyroid hormone in the blood causes the reaction to go in the direction of increased production of hormone. When a certain blood level is reached the reaction goes in the other direction and hormone storage in the follicles occurs. Self-regulation thus emerges. The delivery of hormone to the blood is probably in the nature of a splitting down of thyroglobulin: the storage in follicle, of building up—a reversible enzyme controlled reaction.

But nature was not satisfied with such a simple regulation. A master endocrine was likewise evolved, which would receive stimuli from the nervous system and transmit them on humorally to the endocrine [52]—a superior type of regulation became imposed upon the thyroid—and the pituitary-thyroid axis came into being. Of the evolution of the pituitary's thyroid stimulating hormone, I suppose we know next to nothing. We don't even know its chemical constitution beyond that it is a protein. However, we do know that it exists, and somewhat about how it works..

As Rawson has shown, it impinges on the oxidative enzyme system of the thyroid cell, perhaps in the capacity of a co-enzyme, and in so doing occasions acceleration, not only of cellular oxidation, but of cellular secretory activity as well. Presumably the oxidative enzyme system of the thyroid cell, and its secretory system, are part and parcel of a single functional cellular organization. Under the impact of TSH the thyroid cells not only increase their function, but undergo such structural change as is demanded by this increased function. In the act of causing such stimulation, TSH becomes oxidized and physiologically inert, and is excreted in that form in the urine. But it can be reactivated by reducing agents, and its physiological activity restored. When the thyroid is rendered incapable of responding to TSH through disease, then TSH appears in its active form in the urine.

Surfeiting the thyroid with, or depriving it of iodine produces results which throw light on its physiology. Iodine want, as Marine [53] showed years ago, causes hyperplasia for a time, but with gradual failure of hormone production and finally involution and exhaustion of the thyroid. It is a hyperplasia of frustration. Excess of iodine in the normal has little or no effect. The thyroid uses what it needs and lets the rest pass by.

In the thyrotoxicosis of Graves' disease, however, iodine has a remarkable effect. Here again the thyroid is hyperplastic, but is putting out excess of hormone. The cause of this hyperactivity is unknown. It could be due to a morbid stimulation of the thyroid (as by an excess of TSH) or it could be the result of an abnormal sensitivity of the thyroid to normal stimulation. Still a third possibility is that the thyroid hormone's end-organs have gone hay-wire and call for extra hormonic stimulation. I think the first of the three is the most probable. In any event, what happens when one gives iodine is obvious enough. The thyroid traps an unusually large amount of iodine, it stores thyroglobulin in its follicles and the basal metabolic rate and thyrotoxicosis decline. At the same time less TSH is inactivated and more excreted unchanged in the urine. Seemingly raising the concentration of iodine in the blood acts as a barrier to the discharge of hormone to the body, probably by reversing in some fashion the reversible reaction involved. After a time the barrier may be forced and thyrotoxicosis, in some measure, return.

Why iodine in excess does not have a comparable effect on the normal gland, I do not know. The element of morbid stimulation is apparently necessary to the Graves' type of response.

The effects of cyanides, cyanates, sulfa compounds, and so forth, on the pituitary-thyroid axis, and the fact that all can be forestalled by thyroid, but not all by iodine, opens up a new and important approach to thyroid physiology. Presumably these agents interrupt the enzyme systems of the thyroid, some at one point, others at other points. The result in all, is that hormone output is blocked and the resulting hypothyroidism causes stimulation of the pituitary, which in turn causes hyperplasia of the thyroid. In any case thyroid, and in that of cyanates and cyanides, iodine, will prevent this pituitary stimulation.

I am sure as I now close that you will have the feeling that our knowledge of thyroid physiology is very fragmentary. That is true, of course, but there are some beautiful leads to follow—for example, the rate of manufacture of TSH by the pituitary, the manner in which the pituitary is stimulated to make it, the manner in which the pituitary is inhibited by thyroid hormone, and also whether iodine as such affects the pituitary or whether it is the diphenyl-ether-alanine nucleus which is important. The questions, moreover, of whether TSH has other end-organs than the thyroid epithelium, and how thyroid hormone acts on its end-organs, are likewise intriguing. Finally, I venture to predict that more study of comparative endocrinology or even of paleoendocrinology will be productive. I hope that some of you will tackle some of these problems.

BIBLIOGRAPHY

1. SALTER, W. T.: The endocrine function of iodine, 1940, Harvard University Press, Cambridge.

2. MAGNUS-LEVY, A.: Ueber den respiratorischen Gaswechsel unter dem Einfluss der Thyroidea sowie unter verschiedenen pathologischen Zuständen, Berl. klin. Wchnschr., 1895, xxxii, 650.

3. CANNON, W. B., and CATTELL, McK.: Studies on the conditions of activity in endocrine glands. The secretory innervation of the thyroid gland, Am. Jr. Physiol., 1916, xli, 58.

4. VOGT, M.: Zur Frage der nervösen Regulation der Schilddrüsentätigkeit, Arch. f. exper. Path. u. Pharmakol., 1931, clxii, 129.

5. MARINE, D., and LENHART, C. H.: The pathological anatomy of the human thyroid gland, Arch. Int. Med., 1911, vii, 506.

6. UHLENHUTH, E.: Die Morphologie und Physiologie der Salamander-Schilddrüse, Ent-wcklngsmechn. d. Organ., 1927, cix, 611.

7. ALGIRE, G. H.: The study of the living thyroid gland, Bull. School Med. Univ. Maryland, 1939, xxiii, 211.

8. WILLIAMS, R. G.: Microscopic studies of living thyroid follicles implanted in transparent chambers installed in rabbit's ear, Am. Jr. Anat., 1937, lxii, 1.

9. RIENHOFF, W. F.: Microscopic changes induced in thyroid gland by oral administration of desiccated thyroid. Use of the substance in treatment of congenital and simple colloid goiter, Arch. Surg., 1940, xli, 487.

10. BAUMANN, E.: Ueber das normale Vorkommen des Jods im Thierkörper. III. Der Iodgehalt der Schilddrüsen von Menschen und Thieren, Ztschr. f. physiol. Chem., 1896, xxii, 1.

11. KENDALL, E. C.: The isolation in crystalline form of the compound containing iodin which occurs in the thyroid. Its chemical nature and physiological activity, Trans. Assoc. Am. Phys., 1915, xxx, 420.

12. HARINGTON, C. R., and BARGER, G.: Chemistry of thyroxine. III. Constitution and synthesis of thyroxine, Biochem. Jr., 1927, xxi, 169.

13. GUDERNATSCH, J. F.: Fütterungsversuche an Amphibienlarven, Zentralbl. f. Physiol., 1912, xxvi, 323.

14. UHLENHUTH, E.: Relation between thyroid gland, metamorphosis, and growth, Jr. Gen. Physiol., 1919, i, 473.

15. HARINGTON, C. R., and SALTER, W. T.: The isolation of l-thyroxine from the thyroid gland by the action of proteolytic enzymes, Biochem. Jr., 1930, xxiv, 456.

16. LERMAN, J., and SALTER, W. T.: The maintenance requirements of myxedema patients. Clinical and chemical assay of commercial thyroid preparations, Jr. Pharmacol. and Exper. Therap., 1934, l, 298.

17. SALTER, W. T., and PEARSON, O. H.: The enzymic synthesis from thyroid diiodotyrosine peptone of an artificial protein which relieves myxedema, Jr. Biol. Chem., 1936, cxii, 579.

18. SALTER, W. T., and LERMAN, J.: The genesis of thyroid protein. Clinical assays of artificial thyroid protein in human myxedema, Endocrinology, 1936, xx, 801.

19. REINEKE, E. P., and TURNER, C. W.: Thyroidal action of synthetic thyroprotein, Jr. Clin. Endocrinol., 1943, iii, 1.

20. PLUMMER, H. S.: Interrelationship of function of the thyroid gland and of its active agent, thyroxin, in the tissues of the body, Jr. Am. Med. Assoc., 1921, lxxvii, 243.

21. GERARD, R. W., and McINTYRE, M.: The effect of thyroid feeding on tissue respiration, Am. Jr. Physiol., 1933, ciii, 225.

22. DAVIS, J. E., and HASTINGS, A. B.: Relation of thyroxine to the metabolism of tissues, Jr. Am. Med. Assoc., 1935, civ, 252.

23. McEACHERN, D.: The metabolism of isolated surviving tissues from animals rendered hyperthyroid with thyroxine, Bull. Johns Hopkins Hosp., 1935, lvi, 145.

24. SALTER, W. T., and CRAIGE, F. N.: Vicarious metabolic response. The oxygen consumption of surviving tissues in plasma from hyperthyroid organisms, Jr. Clin. Invest., 1938, xvii, 502.

25. CANZANELLI, A., and RAPPORT, D.: The effect of thyroglobulin and related substances on the O₂ consumption of liver in vitro, Endocrinology, 1937, xxi, 779.

26. LERMAN, J.: Iodine components of the blood. Circulating thyroglobulin in normal persons and in persons with thyroid disease, Jr. Clin. Invest., 1940, xix, 555.

27. BASSETT, A. M., COONS, A. H., and SALTER, W. T.: Protein-bound iodine in blood. V. Naturally occurring iodine fractions and their chemical behavior, Am. Jr. Med. Sci., 1941, ccii, 516.

28. CANZANELLI, A., GUILD, R., and RAPPORT, D.: Further observations on the effect of thyroglobulin and thyroxin on the O₂ consumption of tissues in vitro, Endocrinology, 1939, xxv, 707.

29. GALLI-MAININI, C.: Effect of thyroid and thyrotropic hormones upon oxygen consumption (QO₂) of the thyroid of the guinea pig, Endocrinology, 1941, xxix, 674.

30. RAWSON, R. W., STERNE, G. D., and AUB, J. C.: Physiological reactions of the thyroid-stimulating hormone of the pituitary. I. Its inactivation by exposure to thyroid tissue in vitro, Endocrinology, 1942, xxx, 240.

31. RAWSON, R. W., GRAHAM, R., and RIDDELL, C.: Personal communication.

32. HERTZ, S., and OASTLER, E. G.: Assay of blood and urine for thyreotropic hormone in thyrotoxicosis and myxedema, Endocrinology, 1936, xx, 520.

33. RAWSON, R. W., GRAHAM, R., and RIDDELL, C.: Physiological reactions of the thyroid stimulating hormone of the pituitary. II. Effect of normal and pathologic human thyroid tissue on TSH activity, ANN. INT. MED., 1943, xix, 405–414.

34. HERTZ, S., ROBERTS, A., and EVANS, R. D.: Radioactive iodine as an indicator in the study of thyroid physiology, Proc. Soc. Exper. Biol. and Med., 1938, xxxviii, 510.

35. HAMILTON, J. G., and SOLEY, M. H.: Studies in iodine metabolism by the use of a new radioactive isotope of iodine, Am. Jr. Physiol., 1939, cxxvii, 557.

36. LEBLOND, C. P., SÜE, P., and CHAMORRO, A.: Passage de l'iode radioactif (I *128) dans la thyroïde d'animaux sans hypophyse, Compt.-rend. Soc. de biol., 1940, cxxxiii, 540.

37. MANN, W., LEBLOND, C. P., and WARREN, S. L.: Iodine metabolism of the thyroid gland, Jr. Biol. Chem., 1942, cxlii, 905.

38. HAMILTON, J. G., SOLEY, M. H., and EICHORN, K. B.: Deposition of radioactive iodine in human thyroid tissue, Univ. California Publ., Pharmacol., 1940, i, 339.

39. HERTZ, S., and ROBERTS, A.: Radioactive iodine as an indicator in thyroid physiology. III. Iodine collection as a criterion of thyroid function in rabbits injected with thyrotropic hormone, Endocrinology, 1941, xxix, 82.

40. HERTZ, S., ROBERTS, A., and SALTER, W. T.: Radioactive iodine as an indicator in thyroid physiology. IV. The metabolism of iodine in Graves' disease, Jr. Clin. Invest., 1942, xxi, 25.

41. HERTZ, S., and ROBERTS, A.: Radioactive iodine as an indicator in thyroid physiology. V. The use of radioactive iodine in the differential diagnosis of two types of Graves' disease, Jr. Clin. Invest., 1942, xxi, 31.

42. HUNT, R.: Standardization of thyroid preparations, Arch. Int. Med., 1925, xxxv, 671.

43. CHESNEY, A. M., CLAWSON, T. A., and WEBSTER, B.: Endemic goiter in rabbits. I. Incidence and characteristics, Bull. Johns Hopkins Hosp., 1928, xliii, 261.

44. MARINE, D., BAUMANN, E. J., WEBSTER, B., and CIPRA, A.: The occurrence of antigoitrous substances in plants, Jr. Exper. Med., 1933, lvii, 121.

45. RAWSON, R. W., HERTZ, S., and MEANS, J. H.: Cyanate goiter in man. Report of a case with histological and metabolic studies, Jr. Clin. Invest., 1942, xxi, 624.

46. KOBACKER, J. L.: Production of goiter and myxedema by sulfocyanates, Ohio State Med. Jr., 1942, xxxviii, 541.

47. MACKENZIE, J. B., and MACKENZIE, C. G.: The effect of "sulfa" drugs on the thyroid gland in rats and mice, Fed. Proc., 1942, i, 122.

48. MACKENZIE, C. G., and MACKENZIE, J. B.: Effect of sulfonamides and thioureas on the thyroid gland and basal metabolism, Endocrinology, 1943, xxxii, 182.

49. ASTWOOD, E. B., SULLIVAN, J., BISSELL, A., and TYSLOWITZ, R.: Action of certain sulfonamides and of thiourea upon the function of the thyroid gland of the rat, Endocrinology, 1943, xxxii, 210.
50. ASTWOOD, E. B.: Personal communication.
51. MEANS, J. H.: The nature of Graves' disease with special reference to its ophthalmic component, Am. Jr. Med. Sci., In press.
52. LAMBIE, C. G.: The thyreotrophic hormone and its relation to clinical syndromes, Med. Jr. Australia, 1939, ii, 819 and 853.
53. MARINE, D.: On the occurrence and physiological nature of glandular hyperplasia of the thyroid (dog and sheep), together with remarks on important clinical (human) problems, Bull. Johns Hopkins Hosp., 1907, xviii, 359.

RADIO–PHOSPHORUS—AN AGENT FOR THE SATISFACTORY TREATMENT OF POLYCYTHEMIA AND ITS ASSOCIATED MANIFESTATIONS; A REPORT OF A CASE OF POLYCYTHEMIA SECONDARY POSSIBLY TO THE BANTI'S SYNDROME *

By Lowell A. Erf, M.D., and Harold W. Jones, M.D., F.A.C.P.,

Philadelphia, Pennsylvania

Polycythemia is a disease of unknown etiology characterized by a chronic course and a marked increase in total blood volume over the normal, with an absolute increase in the total number of red blood cells (and often of white blood cells and of platelets).

In a previous paper [1] evidence was presented that marked clinical and hematological improvement occurred in six cases of polycythemia, following administration of radio-phosphorus (p [32]). Those six patients have been maintained in essentially complete clinical and hematological remissions for nearly two years.[2] Four of the six patients have required no radio-phosphorus additional to that described in the previous paper, whereas one † has had one intravenous injection and another has had two courses of three injections each of radio-phosphorus. With the above evidence, plus the evidence presented in this paper which describes the treatment of an additional 11 cases of polycythemia, it would appear that radio-phosphorus is probably the most conveniently administered and the most satisfactory therapeutic agent known at the present time for the treatment of polycythemia. Others [3, 4] have expressed somewhat similar opinions.

Materials and Technics

All of the radio-active phosphorus ‡ solutions were injected intravenously. The variations in dosages were due to the inability to obtain radio-phosphorus at regular or specified intervals of time because of conditions beyond our control, and do not represent a planned régime. The majority of the total dosages varied between 7 and 11 millicuries. As was pointed out in the first paper,[1] since the average life span of the human red cell is approximately 60 to 100 days, the first significant hematological responses occurred about 60 to 100 days after the first injection of radio-phosphorus. It is interesting to note that Head [21] observed three remissions in a typical case of poly-

TABLE I

Treatment of Polycythemia with Radio-Active Phosphorus

Patient	Date of Admission	Chief Complaints and their Duration	Treatment-Response before & during admis.	Physical Findings on Admissions	Lab. Findings on Admissions — Hgb(%)	R.B.C.(mill)	W.B.C.(thous)	Plat.(thous)	Retic.(%)	Hematocrit	Bl.Vol.(cc/kilo)	M.C.V.	Sternal Aspiration
1. E.Bra. Female Age 56 English School teacher 99 lbs.	11-20-54	Pain in upper left.quad.-4 mo. Generalized exzematoid, itching rash-Acne Uriticgta Polycythemia-2 yrs. Vomiting -2 yrs. Dandruff -2 yrs. Weakness & fatigue -2 yrs. Staggering-1 yr. Intense heddaches-2 yrs. Insomnia- 2 yrs. Arthritis ? - 1yr.	Solves & ultra-violet irradiation. Sedatives X-radiation-unsatisfactory Phenylhydrazine therapy started	Thin, emaciated, florid individual Generalized maculopapular eruption Noticeable plexis of enlarged veins on arms and legs Spleen-6cm. below costal margin Liver-3cm. Palms of hands red	112	8.5	32.0	500	2.0	71			
	3-3-39	Same as above–Plus: Pain-(boring in nature) in hands and feet. Arthritis worse ?	Phenylhydrazine-poor response Venesection	Same as above–Plus: Spleen extended inferiorly for 10cm	118	7.5	18.0	542	0.4	67	112	97	
	11-19-41	Same as above.	Phenylhydrazine-fair response Venesection Fowler's solution	Same as above	100	5.5	21.0						
	12-4-41	Same plus- Lumbar pain bilaterally Bleeding from kidneys Bleeds easily when she cuts herself Cramps in fingers and toes		Same-plus: Spleen reached iliac crest Wt.-110 lbs.	99	5.03	25.0	300	1.0	69	110	Ess.Normal	
2. S.Geg. Female Age 62 Scandinavian Dressmaker 126 lbs.	7-23-38	Dizziness-6 yrs. Precordial pain-1yr. Pain in "left side"-1yr. Shaking movements of hands & feet-6yrs. Incontinent at times Arthritis ? Sleepiness	Venesection Phenylhydrazine started	Thin poorly developed, but florid. Mucous membranes deep purple. Spleen 3cm. Liver 2cm. Inguinal & axillary lymph nodes palpable. Palms of hands red	130	11.5	15.0	200					
	12-10-40	Same as above–Plus: Mental confusion Weakness	Same-Plus: Fowler's solution-poor response	Some-Plus: Spleen- 8 cm. Liver-4cm.	128	11.0	12.0	134	2.6				
	10-12-41	Same as above–Plus: Headache Bloody diarrhea Pains in hands and feet	Phenylhydrazine-fair response	Emaciated Veins of arms & legs markedly prominent	90	8.5	6.0			69	180	69	
3. S.Le G. Female Age 60 American Schoolteacher 110 lbs.	3-20-43	Weakness-progressive-1yr. Floridness- 20 yrs Father & grandfather very florid. Father died following craniotomy for relief of "cerebral hemorrhage"	Phenylhydrazine-poor response	Small, slender, very florid. Conjunctiva & oral membranes markedly conjested. Palms of hands very red. Prominent veins. Spleen-2cm below left costal margin	162	7.8	19.9	156	0.4	75	166	Ess.Normal 100	
4. M. Mac C Male Age 64 American Bricklayer 145 lbs.	1-10-43	Gnawing pain in abdomen. Dizziness -1yr. Floridness-20yrs. Single episode of unconsciousness. 1 day before admission. Father & grandfather apparently had polycythemia. Pt. remembers both as very florid & in later yrs grandfather had to be bled every 2mo. to maintain good health	None	Thin, nervous, florid individual. Palms of hands red. Veins prominent	145	9.5	11.9	328	0.5	75	204	Ess.Normal 79	

TABLE I (*Continued*)

Date - Amt. of radioactive Phosphorous admin I.V. in millicuries	No. of mo. after initial treatment with Radio-active Phosphorous.	Physical Findings	Laboratory Findings									Comments
			Hg(%)	RBC(mill)	WBC(thous)	Plat(thous)	Retic(%)	Hematocrit	Bl.Vol(cc/Kilo)	Sternal Aspiration	MCV	
12-4-41 2.8												
12-10-41 2.8												
12-15-41 1.5												
7.1 Total												
No other medication Advised not to eat eggs or red meat.	1-14-42 1 mo.	Rash clearing Spleen 5cm	83	4.19	4.4	115	0.3	45				No pain in upper left quad.
	4-13-42 4 mo.	Rash about gone Neither spleen nor liver palpable	65	3.5	5.5							No complaints
8-24-42 1.5 / 8.6 Grand Total	8-29-42 8 mo.	No skin lesions or symptoms Neither spleen nor liver palpable	78	4.25	5.0	120	0.2	35	107	Ess. Normal		Patient jubilant - first time she has felt well in 8 yrs. Gained strength & wt. (now 116 lbs) No rash or itch Prominence of Veins disappeared Working first time in 8 yrs. Excellent appetite Age 64
	10-13-42 10 mo.		72	4.4	4.4							
	12-22-42 12 mo.		69	3.4	64	188						
	1-11-43 13 mo.		75	3.4	7.4		35	86			102	
	4-22-43 16 mo.		76	4.05	7.1							Feels better than in past 10 yrs Weight - 138 lbs
	5-20-43 17 mo.		75	4.18	7.2	150	39	104			97	Works daily No complaints Weight 139 lbs Age 65
11-1-41 3.5												
11-8-41 2.0	12-9-41 1 mo.	Spleen-2cm Tongue-loss red. Lymph nodes not palpable.	102	8.24	5.0			57				First time in 7 years patient feels like staying awake after 8 P.M.
11-15-41 .8 / 6.3 Total	2-7-42 3 mo.	Mucous membranes normal color	97	6.14	4.0	180	0.2	46			77	Gastric hemorrhage thought to be due to ruptured varicies
Patient advised not to eat red meat or eggs	6-24-42 7 mo.	Neither spleen nor liver palpable	80	4.73	4.8	126.	27	78				
	8-12-42 9 mo.	Prominence of veins has disappeared.	66	4.85	5.3							Feels fine No complaints Wt 146 lbs Age 66 Good appetite.
	12-1-42 *Patient was seen by a physician elsewhere, who gave her iron, echinacea, and quinine. We estimate that she took between 7 and 10 gms of iron during Dec.*											
1-9-43 2.0	1-9-43 14 mo		106	7.7	8.9							
3-10-43 1.2	3-24-43 16 mo	Spleen-3cm below costal margin.	118	9.5	10.			64				Complains of dizziness & odema of ankles. 500 cc blood withdrawn.
4-7-43 2.0	3-31-43		102	8.15	8.0	66	14	133	66			500 cc of blood withdrawn
4-14-43 .8	4-7-43						55					500 cc of blood withdrawn
4-21-43 .4	4-14-43		89	6.9	9.5							500 cc of blood withdrawn
5-1-43 1.6 / 8.0 Total	4-21-43 17 mo.		91									500 cc of blood withdrawn
	5-1-43	Spleen no longer palpable	87	5.8	5.4		45	91				Feeling much better Wt. 144 lbs. No dizziness or odema of ankles.
6-8-43 3.0 / 17.3 Grand Total	6-8-43 19 mo		83	5.3	5.5				84			Works daily No complaints. Wt 144 lbs. Age 67
3-20-43 1.8												
3-22-43 1.5	5-1-43 1½ mo.		122	7.1	9.0							Less florid - Regained strength.
3-24-43 .4												
4-17-43 3.	5-22-43 2 mo.	Spleen not palpable. Veins no longer prominent.	116	5.67	3.7	86	0.2	60		Hypoplastic	107	Nearly normal complexion No complaints Very happy about marked physical improvements. Wt 112 lbs
5-17-43 1.6 / 8.3 Total	6-12-43 3 mo.		106	5.23	6.50	116		53				Normal complexion Works daily without fatigue
2-1-43 4.0	4-7-43 2 mo.		99	6.8	5.4							Gained nearly 50 lbs. Wt 189 lbs Voracious appetite. Feels very well. No complaints.
2-3-43 1.5												
2-24-43 2.3												
3-10-43 1.5	5-1-43 3 mo.		87	5.5	7.0					Ess. Normal		
4-7-43 .6												
4-21-43 .24	6-5-43 4 mo.	Spleen not palpable Veins no longer prominent.	77	3.95	7.0	136	0.3	35	91		89	Lays bricks daily without complaint Complexion normal Wt. 186 lbs.
5-1-43 1.1 / 11.24 Total												

TABLE I *(Continued)*

5. M. Muir Female Age 30 American Housewife 120 lbs.	8-19-40	Abdominal mass. L upper quad. Dizziness, Headache, Stumbling. All of 3-4 months duration.	Phenylhydrazine not tolerated. Fowler's solution	Sclera & conjunctiva injected. Emaciated & florid. Veins prominent. Spleen 8cm. Bl Pr 110/68.	122, 9.2, 13.0	64		74
	12-17-40	Diagnosed Multiple Sclerosis and polycythemia	Course of X-radiation R̥ given— Dec. 1940, April,1941, Oct.1941		95, 52, 7.0	5+	220(?)100	Ess. Normal
	10-5-42	Same as above.	Same as above:		129, 7.7, 12.0, 204	60 220(?) 100		
6. H. Meiz. Male Age 58 Hebrew Tailor 147 lbs.	2-3-43	Weakness, Dizziness, Abdominal pain, Indigestion. All of 5 yrs duration	Frequent venesection. Often as once a mo during the year preceeding admission. Last venesection 2 days before adm. Phenylhydrazine	Thin, emaciated but pale individual. Dark complexioned. Prominent veins on arms and legs.	51, 6.4, 12.0, 300	.7, 32, 92		50
7. R. Mou. Male Age 54 German Janitor 136 lbs	8-23-41	Mass & pain in upper left quadrant, preventing pt. from lying down for 6 mo. Weakness & fatigue. Loss of weight-30 lbs during previous yr. Vomited large amounts of blood in 1939 & again March 1941. Had not worked for 2 yrs. because of weakness & severe attacks of pain in "l. side", probably due to repeated splenic infarcts.	4 courses of x-radiation since 1937. Phenylhydrazine previous year. Fowler's solution. No satisfactory response to any of these.	Thin, emaciated florid. Prominent veins in arms & legs. Spleen reached iliac crest. Infarct present. Spleen tender. Liver 3cm. Tongue beefy & red. Palms of hands red.	99, 8.6, 31, 220	1.9, 54, 112		Hyperplastic. Normal Diff. 57
8. A. Mus. Male Age 56 Ukranian Janitor 121 lbs.	4-24-42	Gnawing pain in abdomen. Nausea & vomiting-1 yr. Weakness-2 yrs. Wt. loss- 20 lbs. in 1 yr. Headache - 2 yrs. Had not worked for nearly 2 yrs because of symptoms	Had received "Stomach ulcer treatment" for past year.	Thin, emaciated, florid. Prominent veins in arms & legs. Mucous membranes deep purple. Spleen & liver- 3cm.	154, 11.0, 10, 242	74, 210		Ess. Normal 65
9. J. Nag. Male Age 41 American U.S. Navy 122 lbs.	4-13-42	"Weakness & heaviness"- 2 yrs. "Fullness in head" headache-2 yr. Attacks of pain in upper left quadrant-1 yr. Indolent ulcers of rt. leg-2 yrs. R.B.C. over 8 million-2 yrs. Unable to work-2 yrs.	X-radiation and phenylhydrazine both made patient sick.	Thin, emaciated, florid. Prominent veins on arms & legs. Large indolent ulcer- 3 cm. Mucous membranes deep purple. Liver-2 cm.	138, 8.5, 13, 220	1.2, 75, 320(?)		Ess. Normal 86
10. I. Udell. Male Age 60 Hebrew Glassgrinder 178 lbs.	7-8-42	Weakness & headache-8 yrs. Burning feet & painful toes-2 yrs. Unable to pick up small objects. with fingers. Has not worked for 4 yrs.	X-radiation. Ultra-violet radiation to skin. Venesection. Poor response	Plethoric, well nourished, ruddy. Mucous membranes purple hue. Large toes red & very tender. Spleen 2cm.	165, 10.0, 10, 252	0.4, 70, 250		Ess. Normal 70
11. O. Wel. Female Age 51 Amer. Negro Maid 100 lbs.	5-4-42	Weakness-8 yrs. Fatigue-8 yrs. Headache-3 yrs. Pains in hands & feet-2 yrs. Backache-2 yrs. Insomnia-2 yrs. Nervousness-8 yrs.	X-radiation-small amts. Ultra-violet irradiation of auto-transfused blood. Fowler's solution. Poor response	Thin, emaciated colored maid. Mucous membranes purple hue. Prominent veins in arms & legs. Spleen just palpable.	126, 11.0, 14, 104	76, 200		Ess. Normal 76

cythemia vera which occurred in each instance, three months following application of radium.

Of the 11 patients, six were white males (two Russian Hebrews), four were white females, and one was a colored female. Each patient had had polycythemia from two to eight years or more before therapy with radioactive phosphorus was instituted. The course of polycythemia varies markedly.[5] All had received many types of therapy previous to radio-phos-

TABLE I (*Continued*)

Dates / Dose	Follow-up	Physical findings	Values	Comments
10-9-42 3.65 10-26-42 1.2 4.85 Total	1-11-43 3 mo. 3-18-43 5 mo. 5-6-43 7 mo.	Spleen not palpable Normal complexion	78 3.69 5.0 74 4.6 6.8 80 5.3 10.3	No complaints except for unsteady gait.
2-3-43 1.0 4-28-43 .55 1.55 Total	4-28-43 2 mo. 6-9-43 4 mo.	Spleen 3 cm. below left costal margin Spleen 3 cm. below left costal margin	61 5.5 7.8	Wt. 148 lbs. Wt 148 lbs T.B. Splenitis (?)
10-2-41 3.7 10-9-41 2.8 10-16-41 1.0 7.5 Total No other medication Advised not to eat eggs or red meat	11-12-41 1 mo. 12-12-41 2 mo. 12-25-41 12-26-41	Spleen 8 cm No tenderness Spleen 4 cm. Prominence of veins disappeared. Pt was feeling fine. No complaints. Wt. 157 lbs. Worked daily without discomfort. Pt. suddenly died elsewhere following large gastric hemorrhage. Post-mortem could not be obtained.	98 5.0 3.3	First time patient could lie down in bed for 6 mo Patient started working.
4-15-42 1.3 5-2-42 7.3 5-25-42 2.4 11.0 Total No other medication. Advised not to eat red meat or eggs.	6-3-42 2 mo. 8-5-42 3 mo. 1-11-43 7 mo. 6-11-43 14 mo.	Gained 5 lbs. Neither spleen nor liver palpable. Gained 20 lbs. Tongue normal color. Prominence of veins disappeared. Normal complexion.	135 9.1 3.0 61 Ess. Normal 78 91 5.9 6.0 41 135 82 4.1 7.2 40 88 81 85 4.4 7.0	No "stomach trouble". Started to work. Voracious appetite. No complaints. Feels "wonderful" Working hard & does not tire. Wt. 141 lbs. Wt. 145 lbs. Has worked daily for 1 yr. without complaints.
4-13-42 1.5 4-17-42 2.6 4-22-42 2.2 8-8-42 4.5 10.8 Total No other medication. Advised not to eat red meat or eggs.	8-8-42 4 mo. 10-22-42 6 mo. 1-18-43 9 mo. 3-3-43 11 mo.	Leg ulcer completely healed. Neither spleen nor liver palpable. Prominence of veins disappeared. Normal complexion.	83 4.38 9.0 44 110 Ess. Normal 91 68 3.86 77 4.39 80 4.14 7.0	Pt. feels fine, but still complains of some weakness. Wt. 138 lbs. Works daily but complains of weakness Works daily without complaints. Feels that he is "completely cured"
7-15-42 2.6 7-17-42 5.6 8-7-42 3.1 11.3 Total No other medication. Advised not to eat red meat or eggs.	8-12-42 1 mo. 9-23-41 2 mo.	Spleen not palpable Pain & redness in toes disappeared. Normal complexion	122 7.6 5.0 142 57 195 60 5.23	No complaints, no headaches Wt 180 lbs. No complaints. Moved to another city.
5-4-42 9.3 5-21-42 2.2 11.5 Total No other medication. Advised not to eat red meat or eggs.	5-21-42 3 wks. 8-29-42 4 mo. 10-13-42 6 mo.	Neither spleen nor liver palpable. Prominence of veins disappeared.	126 10.92 + 76 61 3.47 + 140 0.8 31 99 91 66 4.62	Pt. states that she feels better than in past 20 yrs. No headaches. Sleeps well. Voracious appetite. Wt. 128 lbs.

MHSpringer '45

phorus, such as roentgen-radiation, ultra-violet irradiation to skin or to auto-transfused blood, Fowler's solution, phenylhydrazine, venesection, etc., but none had had satisfactory remissions following such treatments. None had been treated with lead compounds,[6] or spray roentgen therapy.[14] The symptoms varied widely, from those cerebral or spinal in character such as lethargy, dizziness, staggering (multiple sclerosis syndrome), incontinence, etc., to those involving the gastrointestinal tract (symptoms of duodenal and

stomach ulcers and gastric bleeding), the vascular system (tender congested toes, thromboses, varicosities, prolonged bleeding tendencies), the cutaneous system (eczema, acne urticata polycythemic, indolent leg ulcers), the osseous system (arthritis), the urinary system (bloody urine) and the reticulo-endothelial system (splenic infarcts). Two of the patients (cases 3 and 4) presented evidence that polycythemia had probably existed in their families for the two preceding generations. Familial polycythemia is probably identical with polycythemia vera.[7]

Ten of the 11 patients were thin and emaciated * with prominent enlargement of the superficial veins of the arms and legs. All had marked congestion of the mucous membranes, and the hands of each patient (one exception) had decidedly red palms. With one exception secondary polycythemia, such as sclerosis or syphilis of pulmonary vessels, bronchiectasis, tuberculous or syphilitic splenitis, congenital atresia of the aorta, chronic heart lesions, poisonings, etc., were ruled out by histories, by physical examinations, and by hematological, roentgenological, serological and cutaneous tests. Dameshek and Henstell[8] have shown that an iron-poor diet prolonged remissions following venesections of patients with polycythemia. Iron-free diet as a treatment for polycythemia was first proposed by Erhlich.[9] Reznikoff et al.[10] showed in both normal and polycythemic individuals and Cruz et al.[11] in dogs that the iron of old or discarded red cells is reutilized in the formation of new hemoglobin. Because of such information all of the patients were placed on a meat-and-egg-free diet after the first injection of radio-phosphorus.

The pipettes and counting chambers used on these cases were standardized by the United States Bureau of Standards. The hematological technics were those used universally. The blood volume studies were made by the use of 1 per cent Congo red solutions. Wintrobe sedimentation tubes were used to determine the hematocrit levels. Sternal punctures were made by the technic described in 1937[12]; and the sternal marrow findings of the 17 cases of polycythemia presented then were essentially the same as those of the seven patients (before treatment) presented in this paper.

RESULTS

The clinical and hematological findings before and after treatment with radio-phosphorus of 11 cases of polycythemia are presented in table 1.

In table 2 are listed the sternal bone marrow findings before (in eight cases) and after (in eight cases) treatment with radio-phosphorus.

After treatments with radio-phosphorus the patients usually gained weight, developed unusually good appetites and had clinical and hematological remissions. The changes that occurred in associated conditions follow:

* This feature was emphasized by F. Parkes-Weber.[33]

TABLE II

Patient / Date	Total nucleated cells per cu. mm. in aspirated marrow fluid (thous.)	Myeloblasts	Neutrophilic myelocytes	Eosinophilic myelocytes	Neutrophilic metamyelocytes	Polymorphonuclear neutrophiles	Polymorphonuclear eosinophiles	Polymorphonuclear basophiles	Lymphocytes	Plasmocytes	Megakaryocytes	Megaloblasts	Erythroblasts	Normoblasts	Reticulo-endothelial cells	Cells in mitosis	Peripheral red blood cell levels (millions)
E. Bra. 3–14–39 before p³²	50.2	2.2	12.3	1.	21.9	46.6	.67		1.67	.33	.33	2.	3.33	7.33	.6	.66	7.5
8–30–41 after p³²	35.	.3	23.6		20.3	18.6	2.		7.			2.	1.6	23.3		.3	4.2
6–28–43 after p³²	23.	1.0	18.3	1.3	23.3	26.6	2.6		3.3		.6	1.3	2.3	18.3		.6	3.6
S. Geg. 6–28–43 after p³²	10.		18.		25.	23.5			5.0			.5	2.0	25.0	1.5		5.4
LeGrand 3–24–43 before p³²	86.	.6	18.6	2.6	11.6	16.6	2.6	1.03	3.3	.3	1.3	1.3	10.3	29.3	1.0		7.8
6–12–43 after p³²	12.	1.3	6.6	1.0	10.3	31.3	1.0		8.3	2.0	.3		3.3	33.0			5.2
R. M. Mc 1–19–43 before p³²	45.	.5	7.5		15.0	43.0	.5	1.5	5.5	.5		1.3		26.	1.0		9.5
6–24–43 after p³²	24.	.3	20.0	2.0	14.0	26.6	.6		6.6				.3	29.3			3.8
H. Mei 1–19–43 before p³²	13.		11.0	2.0	20.0	36.0	3.0	1.0	2.0		1.0	2.0	1.0	21.			6.4
6–23–43 after "	34.	.3	20.0	.6	13.3	24.1			1.6		.3	2.0	1.6	35.3			5.4
8–10–43 "	115.	2.0	17.	1.3	20.	16.3			3.3		.6	1.3	9.0	27.0			6.0
R. Mou. 9–3–41 before p³²	108.	2.6	12.6	.33	15.6	40.	1.3	1.6	2.6			.33	2.3	20.			8.6
M. Mui 10–8–42 before p³²	74.	.66	16.	1.3	32.6	18.6	4.6		3.6	2.33	.33	.33	2.3	18.	1.0	1.0	7.7
A. Mus. 5–7–42 before p³²	37.	1.	11.	1.6	16.	18.	2.6		4.	.3	.33	3.6	3.3	34.	.1	1.3	11.0
8–27–42 after p³²	32.	.6	19.	.3	11.6	16.3	1.		6.6		.3	2.3	3.3	40.	.3	.6	4.6
6–16–43 after p³²	133.	1.0	12.0	2.6	15.0	18.3	.6		1.6				9.6	35.6		1.0	3.8
J. Nagel 6–21–43 after p³²	21.	.3	11.0	2.6	23.3	26.0	.3		5.0		.6	1.0	.6	28.3	.6		3.9
O. Wel. 5–22–42 before p³²	26.	1.3	25.	.66	13.3	10.	.33		7.3	.66	.66	.66	4.6	35.3	.66	.66	11.0
8–30–42 after "	100.	.33	20.	2.	16.3	13.3	.33		5.	1.3		1.	6.6	33.3	.3		3.4
7–7–43 "	93.		15.	2.	25.	19.	1.		1.6				2.6	31.		1.6	3.7

Fig. 1.   The reproduction (by permission of the authors—see reference 12) of a photograph of patient 1 published in 1939.   The lesions, which were of eight years' duration, were described as acne urticata polycythemic and were responsible for much itching, burning and scaling to the patient.

Fig. 2.   Photograph of same patient in 1942 after treatment with radio-phosphorus. Patient is now free of all cutaneous discomfort.
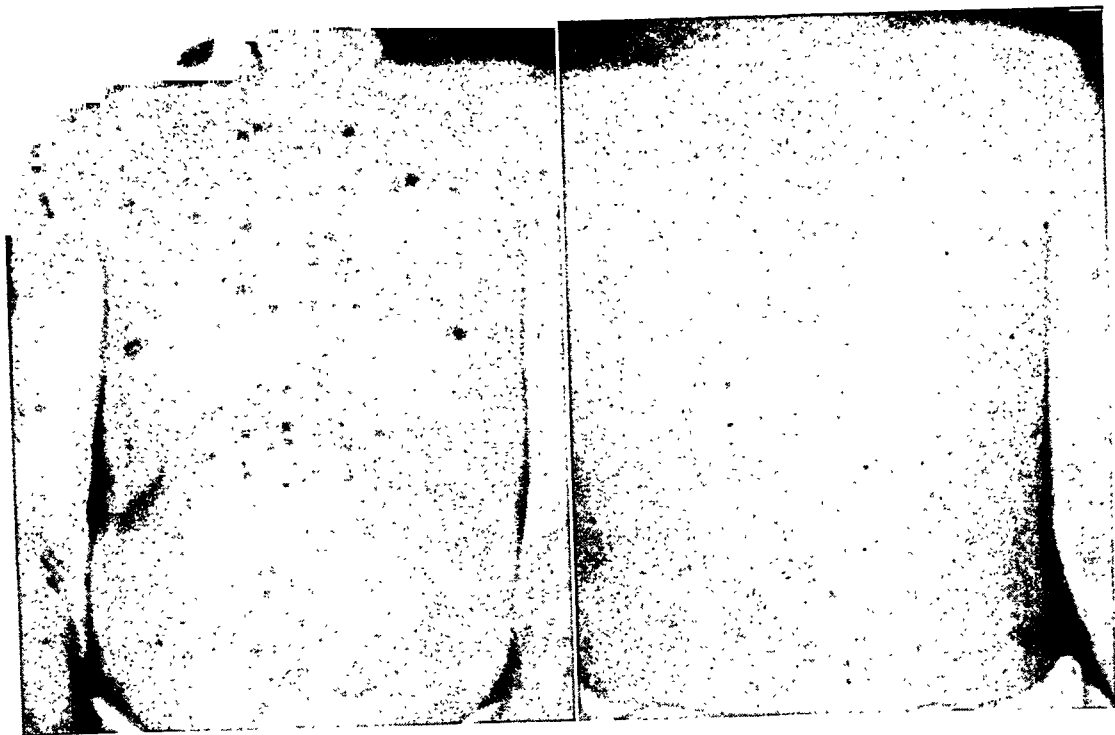
FIG. 3. Photograph of patient suffering from chronic dermatitis herpetiformis of six months' duration before administration of radio-phosphorus. Patient complained of intense itching, burning and scaling.
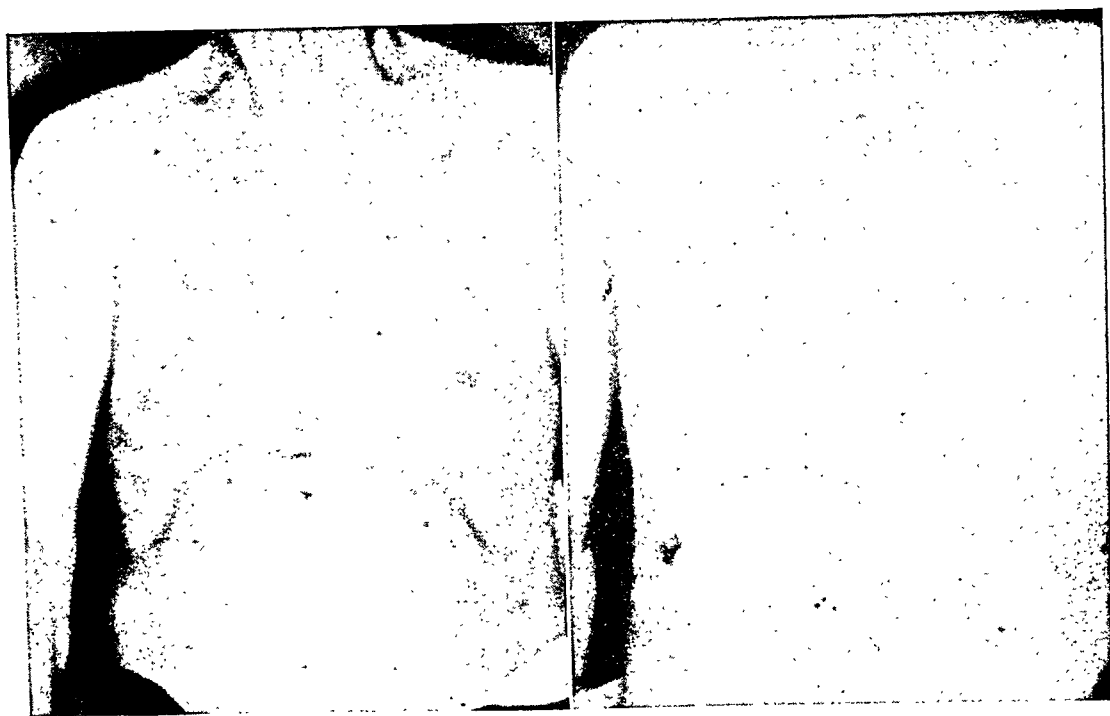
FIG. 4. Photograph of same patient 30 days after p^{32}. All symptoms had disappeared 80 days after p^{32}—no evidence of the former condition could be observed.

a. Skin Conditions. Figures 1 and 2 show the skin of the back of patient 1 before and after therapy with radio-phosphorus. The skin lesions of this particular patient were described in minute detail and termed acne urticata polycythemic by Weidman and Klauder.[18] The lesions which had existed for eight continuous years were generalized and caused almost unbearable itching and burning. Scaling of skin and scalp (dandruff) was profuse. All of these symptoms disappeared completely after treatment with radio-phosphorus, and have not returned for over a year.
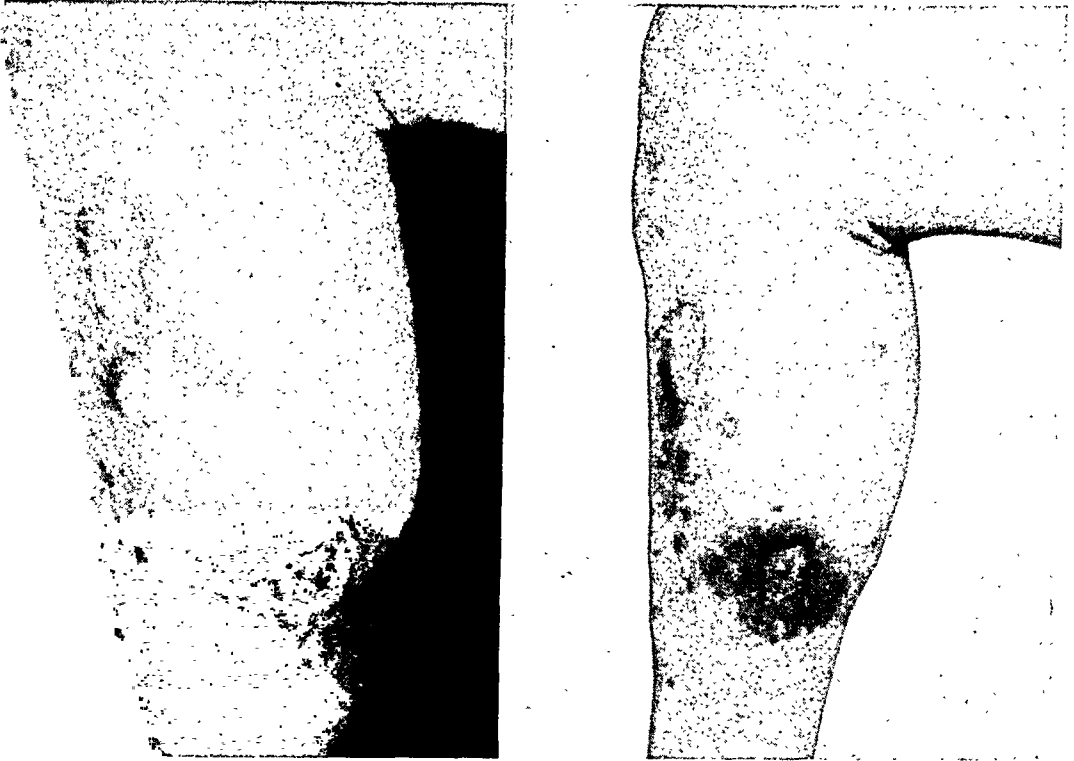
Fig. 5. (*Left*) Photograph of ulcers of leg of patient 9 before radio-phosphorus therapy. These ulcers had been weeping for a period of over two years. No therapy had benefited the patient.

Fig. 6. (*Right*) Photograph of the same leg shown in figure 5 three months after radio-active phosphorus had been administered. Lesions are scarred and no longer weeping.

The improvement of the skin lesions may not have been a result of an improvement of the polycythemic syndrome since another patient, who did not have polycythemia but who had similar lesions (as to appearance, distribution, symptoms and refractoriness to treatment) for a period of six months (diagnosed as chronic dermatitis herpetiformis by the Division of Dermatology, Jefferson Hospital) improved equally well following treatment with radio-phosphorus. Within one week after administration of 2 Mc. of p^{32} the intense itching had disappeared. Figure 3 shows the lesions before, and figure 4 shows the lesions four weeks after injections of p^{32}. Within less than 80 days the lesions had completely disappeared.

We have had two patients with Hodgkin's disease suffering from intolerable generalized itching of the skin who derived complete relief following therapy with p³². The radio-phosphorus probably did not alter the course of the Hodgkin's disease.

FIG. 7. *Case 6.* Focal areas of calcification of the spleen.

Patient 9 had had chronically weeping indolent leg ulcers for over two years with every type of therapy failing until radio-phosphorus was administered. The weeping ceased and within two months after p³² administration the ulcer healed, leaving a pigmented scar (figures 5 and 6). A year later the scar had become softer and continued to remain asymptomatic.

b. *Mean Corpuscular Volume.* The values of the mean corpuscular volume of nine of the 11 cases were below normal, indicating that the red blood

cells of patients with polycythemia are smaller than normal. In eight of nine cases studied the red cells became larger after treatment with p^{32}. Case 2 had a relapse following the unauthorized ingestion of large doses of iron, and simultaneously the mean corpuscular volume decreased. As soon as a remission was reëstablished, however, the mean corpuscular volume became nearly normal.

c. Coagulation Time. The coagulation time of polycythemic blood is abnormally prolonged, and patients bleed readily following minor cuts. This symptom disappeared following therapy with p^{32}.

d. Gastric Hemorrhage. Four of the 10 cases had been informed elsewhere that they had gastric ulcers and three of the patients had had gastric hemorrhages before therapy with p^{32}. Case 7 had had large exsanguinating gastric hemorrhages one and two years before treatment with p^{32}. However, after the blood findings had returned to normal levels and the patient was asymptomatic following treatment with p^{32}, a severe fatal gastric hemorrhage occurred. Case 2 also had a gastric hemorrhage after p^{32} had been started. This patient had a relapse after taking iron and was brought back into a state of remission following phlebotomy and additional treatment with p^{32}, without the occurrence of gastric hemorrhages. For the third case (No. 6) of gastric hemorrhage see addendum.

e. Bone Marrow Findings (see table 2). The differential marrow findings in cases of polycythemia are rather similar to those of normal individuals. Strangely the percentage of the erythropoietic elements is often decreased in number. It is apparent, therefore, that in polycythemia greater quantities of marrow throughout the body become hyperactive. Since the marrow findings (both the total nucleated count and differential) in pretreated cases of polycythemia are nearly within the limits of normal, it is logical that the findings would not be significantly altered following therapeutic doses of radio-phosphorus.

DISCUSSION

The 11 patients reported here plus the six reported previously [1] have stated that the remissions following radio-phosphorus were satisfactory and that no other therapy had given equally satisfactory remissions. It must be brought out here that none of these patients had received spray roentgen therapy which according to many authors [14, 15, 16] gives excellent remissions in polycythemia. The mechanism of these two types of therapy may be similar. Radio-phosphorus concentrates in the bone marrow and continuously bombards such tissues for days.[17, 18] Both p^{32} and roentgen radiation probably decrease red blood cell production by retarding mitosis of normoblasts in early prophase.[19, 20] (Radio-phosphorus is not a red blood cell lytic agent, as is phenylhydrazine, because neither jaundice nor increased excretion of urinary urobilinogen has been observed following administration.) In both types of treatment (radio-phosphorus and spray roentgen radiation) the period of irradiation (by beta particles) is prolonged, which

may be the effective factor. We hope to be able to study these two types of therapy, including the measurement of iron intake and excretion in patients with polycythemia.

CONCLUSIONS

At the present time, in our experience, radio-phosphorus is the most convenient and satisfactory therapeutic agent for the treatment of polycythemia and its associated manifestations.

ADDENDUM

Patient H. M. (No. 6 on table 1) had had five severe gastric hemorrhages (hospitalized elsewhere) during the seven years preceding treatment with radio-active phosphorus. Because he was so fearful of gastric hemorrhages, he gave monthly a pint of blood to the Red Cross during the twelve months preceding his admission to Jefferson Hospital. During that same year he had had several attacks of syncope associated with a drop in blood pressure to as low as 70/40. When we first saw the patient we obtained the history of polycythemia (by letter from a hospital where he had previously been studied), and we felt that the marked hypochromia and microcytosis (hemoglobin 51 per cent, red blood count 6,500,000, and mean corpuscular volume 50) observed on admission were sequelae of the monthly blood donations. However, after months of weekly determinations of blood levels, no changes were noted and we gave the patient iron (adequate doses of ferrous sulfate) expecting that the hemoglobin and red blood cell levels would rise immediately, as occurred in case 2. During the period of the administration of iron, the patient developed two attacks of syncope (a week apart), and the systolic pressure fell into the 70's. In addition, the administration of iron was not followed by a significant elevation in the red blood cell and hemoglobin levels. One of us (L. A. E.) began to suspect the patient had polycythemia, secondary to some other process, and sent the patient to the roentgen-ray department as a possible case of quiescent primary tuberculosis of the spleen (with possible tuberculous involvement of the adrenals). The roentgen-ray department reported large calcified areas in the spleen and indicated that the findings (see figure 7) were compatible with the diagnosis of primary tuberculosis of the spleen.[22, 23, 24] The patient was afebrile. The human tuberculin skin test was negative, but the bovine tuberculin skin test was strongly positive which again was compatible with the suspected diagnosis.[23, 25, 26] Greppi[27] and Fox[28] believe that active primary tuberculosis of the spleen is associated with anemia, the chronic form is associated with polycythemia. Wintrobe[29] states that "about 82 cases (tuberculous splenomegaly) have been reported" by 1942 and also points out that tuberculous processes in the spleens of patients with polycythemia (he has had two cases) are not uncommon.

Gastric hemorrhages in primary tuberculosis of spleen are not unusual,[22, 30, 31, 32, 35] and because of the positive bovine tuberculin test, the roentgenological findings, the persistently low hemoglobin and white blood cell levels, but high red blood cell levels, which were unaltered by iron therapy, the attacks of syncope and the patient's intense fear of additional gastric hemorrhages, splenectomy was agreed upon. Upon opening the abdomen diffuse chronic adhesive peritonitis was strikingly evident, gall stones could be palpated, but the liver grossly revealed no cirrhosis and the spleen was firmly matted with dense adhesions to almost all of the structures located in the area of the upper left quadrant. The veins between the spleen and stomach were unusually large and abnormally abundant. The portal veins and splenic vein could not be thoroughly examined. During the operation 3,000 c.c. of

blood, 3,000 c.c. of saline and 80 grams of dried plasma restored in 250 c.c. of distilled water were necessarily administered. The spleen weighed 1,020 grams and contained, in addition to others, two large (2 by 3 by 1 cm.) calcified plaques about the large veins at the hilum. Pieces of the spleen were emulsified and injected into guinea pigs; other pieces were dried. Several pieces from several sections of the spleen were fixed for microscopic examination. The patient died the third postoperative day (extensive pulmonary edema) and every effort to obtain an autopsy failed.

The microscopic findings of the spleen were unusual in that the typical features of the Banti's syndrome (fibrosis, marked hyperplasia of the reticular cell system, hyaline degeneration of the pulp, etc.) were observed but there was no pathological evidence of tuberculosis; and the typical findings of polycythemia (hypertrophy of pulp, marked congestion with red blood cells, hematopoiesis, etc.) were absent. Weber [33] states that the Banti's syndrome may occasionally be associated with an erythrocyte count above normal (anemia splenica sine anemia) but does not present a case and we have not been able to find an authentic case reported in the literature. Weber speaks of "erythrocytosis secondary to blood stasis" (thrombosis of portal vein, splenic vein, etc.) but Oppenheimer [34] believes that the polycythemia in such cases is primary and the thromboses secondary. It would be difficult to conclude definitely from the pathological evidences found in the spleen, whether the spleen could be classified as one belonging to the Banti's syndrome or as one of long standing polycythemia in which fibrosis and hypertrophy of the reticular cell system were the prominent features. The clinical and pathological evidence together would make one lean towards the diagnosis of the Banti's syndrome.

BIBLIOGRAPHY

1. Erf, L. A., and Lawrence, J. H.: Clinical studies with the aid of radio-phosphorus. III. The absorption and distribution of radio-phosphorus in the blood of, its excretion by, and its therapeutic effect on patients with polycythemia, Ann. Int. Med., 1941, xv, 276.
2. Lawrence, J. H.: Personal communication.
3. Fitz-Hugh, T., Jr., and Hodes, P. J.: Clinical experience with radio-phosphorus in the treatment of certain blood dyscrasias, Am. Jr. Med. Sci., 1942, cciv, 662.
4. Low-Beer, B. V., Lawrence, J. H., and Stone, R. S.: The therapeutic use of artificially produced radioactive substances, Radiology, 1942, xxxix, 573.
5. Rosenthal, N., and Bassen, F. A.: Course of polycythemia, Arch. Int. Med., 1938, lxii, 903.
6. Falconer, E. H.: Treatment of polycythemia vera with lead compounds, Am. Jr. Med. Sci., 1942, cciii, 857.
7. a. Harrop, G. A., Jr., and Wintrobe, M. D.: Polycythemia in Handbook of hematology, 1938, Paul B. Hoeber, Inc., New York, iv, 2366.
   b. Nadler, S. B., and Cohn, I.: Familial polycythemia, Am. Jr. Med. Sci., 1939, cxcviii, 41.
8. Dameshek, W., and Henstell, H. H.: The diagnosis of polycythemia (see appendix), Ann. Int., Med., 1940, xiii, 1360.
9. Harrop, G. A., Jr.: Polycythemia, Medicine, 1928, vii, 291.
10. Reznikoff, P., Toscani, V., and Fullarton, R.: Iron metabolism studies in normal subjects and polycythemic patients, Jr. Nutr., 1934, vii, 221.
11. Cruz, W. O., Hahn, P. F., and Bale, W. F.: Hemoglobin radioactive iron liberated by erythrocyte destruction (acetylphenylhydrazine) promptly reutilized to form new hemoglobin, Am. Jr. Physiol., 1942, cxxxv, 595.
12. Vogel, P., Erf, L. A., and Rosenthal, N.: Hematological observations on bone marrow obtained by sternal puncture, Am. Jr. Clin. Path., 1937, vii, 436–447 and 498–515.

13. WEIDMAN, F. D., and KLAUDER, J. V.: Acne urticata polycythaemic, Arch. Dermat. and Syph., 1939, xxxix, 645.
14. HUNTER, F. T.: Spray x-ray therapy in polycythemia vera, New England Med. Jr., 1936, ccxiv, 1123.
15. REZNIKOFF, P.: Polycythemia, Bull. New York Acad. Med., 1939, xv, 311.
16. PIERSON, J. W., and SMITH, C. D.: Treatment of polycythemia vera by roentgen irradiation of the entire body, Am. Jr. Roent., 1940, xliii, 577.
17. ERF, L. A., and LAWRENCE, J. H.: Phosphorus metabolism in neoplastic tissue, Proc. Soc. Exper. Biol. and Med., 1941, xlvi, 694.
18. ERF, L. A.: Clinical studies with the aid of radio-phosphorus. The retention of radio-phosphorus by tissues of patients dead of leukemia, Am. Jr. Med. Sci., 1942, cciii, 529.
19. MARSHAK, A.: Effect of x-rays on chromosomes in mitosis, Proc. Nat. Acad. Sci., 1937, xxiii, 362.
20. MARSHAK, A.: Effects of x-rays and neutrons on mouse lymphoma chromosomes in different stages of the nuclear cycle, Radiology, 1942, xxxix, 621.
21. HEAD, G. D.: Tuberculosis of spleen with polycythemia and splenomegaly improved by treatment with radium and benzene, Jr. Am. Med. Assoc., 1924, lxxxiii, 40.
22. BUNCH, G.: Primary tuberculosis of the spleen, with report of case simulating Banti's disease, South Med. Jr., 1931, xxiv, 764.
23. SHANDS, H. R.: Chronic primary tuberculosis of the spleen; x-ray diagnosis; case reports, Am. Jr. Surg., 1933, xx, 707.
24. SOLOMON, H. A., and DORAN, W. T., JR.: Primary tuberculosis of the spleen, N. Y. State Jr. Med., 1939, xxxix, 1288.
25. GIFFIN, H. Z.: Tuberculosis of the spleen, Med. Clinics N. Am., 1919, iii, 765.
26. BROWN, J. W., MASON, J. L., and LUCIA, S. P.: Tuberculous splenomegaly: study of a case, Ann. Int. Med., 1942, xvii, 517.
27. GREPPI as quoted by PETHER, G. C.: Tuberculosis of the spleen, Lancet, 1937, ii, 1423.
28. FOX, H.: Silent, so-called primary tuberculosis of the spleen, Am. Jr. Clin. Path., 1939, ix, 549.
29. WINTROBE, M. M.: Clinical hematology, 1942, Lea and Febiger, Philadelphia.
30. FLANDRIN, P.: A new splenic lesion; Gandy Gomna nodules with caseous tuberculous centers; a case, Sang, 1931, v, 271.
31. LOCQUETTE as quoted by HICKLING, R. A.: Tuberculous splenomegaly with miliary tuberculosis of the lungs, Quart. Jr. Med., 1938, vii, 263.
32. ENGELBRETH-HOLM, J.: A study of tuberculous splenomegaly and splenogenic controlling of the cell emission from the bone marrow, Am. Jr. Med. Sci., 1938, cxcv, 32.
33. PARKES-WEBER, F.: Polycythemia, erythrocytosis and erythremia, H. K. Lewis and Co., London, 1921: also Epitome by same publisher, 1929.
34. OPPENHEIMER, B. S.: Vascular occlusion in polycythemia vera, Trans. Assoc. Am. Phys., 1929, xliv, 338.
35. BALFOUR, D. S.: Splenectomy for repeated gastro-intestinal hemorrhage, Ann. Surg., 1917, lxv, 89.

THE TREATMENT OF MENINGOCOCCUS CARRIERS WITH SULFADIAZINE *

By F. S. Cheever, Lieutenant, Medical Corps, U.S.N.R., B. B. Breese, Lieutenant Commander, Medical Corps, U.S.N.R., and H. C. Upham, Ensign, Hospital Volunteer Specialist, U.S.N.R., *Bethesda, Maryland* †

This paper deals with an investigation of the efficacy of sulfadiazine in clearing the nasopharynx of meningococci. Since the meningococcus carrier is generally considered to be the paramount factor in the spread of an epidemic of meningococcal meningitis, any therapeutic agent consistently successful in eliminating the specific organism from the posterior nasopharynx might well prove to be of considerable value in the prophylaxis of the disease. Various members of the sulfonamide group of drugs have given promising results. The original observations of Meehan and Merrilles [1] on the successful use of sulfapyridine have been confirmed by others [2,3] and extended to include sulfanilamide [4] and sulfathiazole as well. [5] For the present study sulfadiazine was the drug of choice because of its low toxicity and the excellent therapeutic response obtained with it in the treatment of clinical cases. A control group of untreated carriers was included so that the specific action of the drug might be truly evaluated.

TABLE I

Results of Nasopharyngeal Cultures on a Sample of the Camp's Population

Total Number Cultured	Type I		Type II		Type II Alpha		Untypable Meningococci		Total Carriers	
	Number	%	Number	%	Number	%	Number	%	Number	%
1004	469	46.7	55	5.5	39	3.9	16	1.6	579	57.7

During the winter of 1942–1943 an outbreak of meningococcal infections occurred in a large naval construction training center. Cases of both meningitis and uncomplicated septicemia were observed; in over 90 per cent of these a Type I meningococcus proved to be the causative organism. The response to sulfadiazine therapy was gratifying in that the mortality rate re-

mained in the neighborhood of 5 per cent. The clinical features of the epidemic are to be reported elsewhere.

A carrier rate determination on a representative sample of the camp's population gave a total incidence of 57.6 per cent, with Type I nearly five times as prevalent as all other meningococci combined (table 1).

The nasopharyngeal cultures were obtained by means of a straight swab and tongue depressor. If they could be brought to the laboratory within two hours the swabs were placed in individual tubes containing 0.5 c.c. of Mueller's starch casein-hydrolysate medium [6] made up in fluid form without agar.* Swabs that had to stand overnight were placed in 0.5 c.c. of sterile horse blood in accordance with Mueller's modification of his own method [7] for

TABLE II

Treated Group:

Type	Initial: 0 Hours		72 Hours		144 Hours	
	No. of Cases	% of Total Cases	No. of Cases	% of Total Cases	No. of Cases	% of Total Cases
Type I............	140	68.96	0	00.00	0	00.00
Other Meningococci..	21	10.35	0	00.00	1	00.49
Total Carriers.......	161	79.31	0	00.00	1	00.49
Negative Cultures....	42	20.69	203	100.00	202	99.51
Total Cases.........	203	100.00	203	100.00	203	100.00

TABLE III

Untreated Group:

Type	Initial: 0 Hours		72 Hours		144 Hours	
	No. of Cases	% of Total Cases	No. of Cases	% of Total Cases	No. of Cases	% of Total Cases
Type I............	101	54.30	135	72.58	123	66.13
Other Meningococci..	7	3.76	15	8.06	19	10.22
Total Carriers.......	108	58.06	150	80.64	142	76.35
Negative Cultures....	78	41.94	36	19.36	44	23.65
Total Cases.........	186	100.00	186	100.00	186	100.00

preserving gonococcal cultures. The starch casein hydrolysate medium * was used for plating; the Petri dishes were then incubated for 16 hours in a candle jar containing a small amount of thoroughly moistened cotton to insure a properly humid atmosphere. After suspicious colonies had been isolated the organisms were typed by the tube agglutination method; those reacting with polyvalent serum alone were run through sugars before being classed as "untypable meningococci."

Men from a barrack known to have a high carrier rate were divided into two approximately equal groups. These individuals lived, worked and

* Each liter of this medium contains 50 mg. of para amino benzoic acid.

TABLE IV

Treated Group:

Type	Initial: 0 Hours		72 Hours		144 Hours	
	No. of Cases	% of Total Cases	No. of Cases	% of Total Cases	No. of Cases	% of Total Cases
Type I............................	140	68.96	0	00.00	0	00.00
Type I becoming other types, or untypable meningococci...............	0	00.00	0	00.00	1	00.49
Type I becoming negative.............	0	00.00	140	68.96	139	68.47
Total................................	140	68.96	140	68.96	140	68.96
Meningococci other than Type I........	21	10.35	0	00.00	0	00.00
Meningococci other than Type I becoming Type I...........................	0	00.00	0	00.00	0	00.00
Meningococci other than Type I becoming negative........................	0	00.00	21	10.35	21	10.35
Total.................................	21	10.35	21	10.35	21	10.35
Negative..............................	42	20.69	42	20.69	42	20.69
Negative becoming Type I.............	0	00.00	0	00.00	0	00.00
Negative becoming meningococci other than Type I.........................	0	00.00	0	00.00	0	00.00
Total.................................	42	20.69	42	20.69	42	20.69
Grand Total.........................	203	100.00	203	100.00	203	100.00

TABLE V

Untreated Group:

Type	Initial: 0 Hours		72 Hours		144 Hours	
	No. of Cases	% of Total Cases	No. of Cases	% of Total Cases	No. of Cases	% of Total Cases
Type I................:..............	101	54.30	95	51.08	75	40.32
Type I becoming other types or untypable meningococci.......................	0	00.00	2	1.07	3	1.61
Type I becoming negative.............	0	00.00	4	2.15	23	12.37
Total.................................	101	54.30	101	54.30	101	54.30
Meningococci other than Type I........	7	3.76	2	1.07	2	1.07
Meningococci other than Type I becoming Type I...........................	0	00.00	1	0.54	1	0.54
Meningococci other than Type I becoming negative........................	0	00.00	4	2.15	4	2.15
Total.................................	7	3.76	7	3.76	7	3.76
Negative..............................	78	41.94	28	15.05	17	9.14
Negative becoming Type I.............	0	00.00	39	20.97	47	25.27
Negative becoming meningococci other than Type I.........................	0	00.00	11	5.92	14	7.53
Total.................................	78	41.94	78	41.94	78	41.94
Grand Total.........................	186	100.00	186	100.00	186	100.00

messed together, and, as far as could be ascertained, were equally exposed to other carriers in the camp. On the first day nasopharyngeal cultures were taken on all men; those in the first group were then given three grams of sulfadiazine in divided doses on the first day and similarly three grams on the second and two grams on the third day, each man thus receiving a total of eight grams over the course of 72 hours. The second group, serving as a control, was left untreated. On the fourth day both groups were recultured and urine specimens obtained from those men who had received the drug. No further medication was given, but on the seventh day another nasopharyngeal culture was taken on each man.

TABLE VI

Treated Group:

At 0 Hour: (Start of Experiment)

Type I (A)		Other Meningococci (B)		Negative (C)		Total	
No. of Cases	% of Total Cases	No. of Cases	% of Total Cases	No. of Cases	% of Total Cases	No. of Cases	% of Total Cases
140	68.96	21	10.35	42	20.69	203	100.00

At 72 Hours:

	Type I		Other Meningococci		Negative		Total	
	No.	%	No.	%	No.	%	No.	%
Type I (A)...............	0	00.00	0	00.00	140	68.96	140	68.96
Other Meningococci (B)...	0	00.00	0	00.00	21	10.35	21	10.35
Negative (C)............	0	00.00	0	00.00	42	20.69	42	20.69
Total..................	0	00.00	0	00.00	203	100.00	203	100.00

At 144 Hours:

	Type I		Other Meningococci		Negative		Total.	
	No.	%	No.	%	No.	%	No.	%
Type I (A).............	0	00.00	1	00.49	139	68.47	140	68.96
Other Meningococci (B)...	0	00.00	0	00.00	21	10.35	21	10.35
Negative (C)............	0	00.00	0	00.00	42	20.69	42	20.69
Total.................	0	00.00	1	00.49	202	99.51	203	100.00

No loss in sense of well being was noted in any of the men given sulfadiazine; no rashes occurred; and microscopic examination of the urine obtained from each individual 12 hours after withdrawal of the drug showed no evidence of hematuria or crystalluria. Unfortunately, facilities for determining sulfadiazine blood levels were wanting.

The results are given in tables 2, 3, 4, 5, 6, and 7.

TABLE VII

Untreated Group:

At 0 Hours: (Start of Experiment)

Type I (A)		Other Meningococci (B)		Negative (C)		Total	
No. of Cases	% of Total Cases	No. of Cases	% of Total Cases	No. of Cases	% of Total Cases	No. of Cases	% of Total Cases
101	54.30	7	3.76	78	41.94	186	100.00

At 72 Hours:

	Type I		Other Meningococci		Negative		Total	
	No.	%	No.	%	No.	%	No.	%
Type I (A).............	95	51.08	2	1.07	4	2.15	101	54.30
Other Meningococci (B)...	1	0.54	2	1.07	4	2.15	7	3.76
Negative (C)	39	20.96	11	5.92	28	15.06	78	41.94
Total..................	135	72.58	15	8.06	36	19.36	186	100.00

At 144 Hours:

	Type I		Other Meningococci		Negative		Total	
	No.	%	No.	%	No.	%	No.	%
Type I (A).............	75	40.32	3	1.61	23	12.47	101	54.30
Other Meningococci (B)...	1	0.54	2	1.07	4	2.15	7	3.76
Negative (C).............	47	25.27	14	7.54	17	9.13	78	41.94
Total..................	123	66.13	19	10.22	44	23.75	186	100.00

All of 161 carriers given 8 grams of sulfadiazine over a period of 72 hours had become negative by the fourth day. After an additional three days during which they received no further treatment, 160 or 99.51 per cent remained negative. The one case which became positive showed a change in type (Type I to Type II alpha) suggesting that it was a new infection rather than a recrudescence of an old one. The control group receiving no treatment during the same period showed a statistically significant increase in the total carrier rate during the first 72 hours, and during the second 72 hours a slight decrease which, however, was not statistically significant. The results may be summarized in table 8.

Ninety men from the company receiving sulfadiazine were subjected to nasopharyngeal cultures on the nineteenth day after the drug had been withdrawn, and a carrier rate of 15.5 per cent was obtained. This process was repeated on the thirty-seventh day and in addition cultures were obtained from 134 men of the control company which had received no specific chemotherapy. During this period both groups had been carrying on their usual duties in camp and had continued to share the same barracks. Among the controls, meningococci were isolated from 81.3 per cent of the cases;

TABLE VIII

Percentage of Total Cultures Positive

Group	Total Population	0 Hours	72 Hours	144 Hours
Treated..	203	79.31	00.00	00.49
Untreated......................................	186	58.06	80.64	76.35

The Treated Group: 8 grams of sulfadiazine per man in the first 72 hours.
The Untreated Group: No specific chemotherapy.
Criterion of Significance: 3 times sigma.

TABLE IX

Results of Nasopharyngeal Cultures on a Sample of the Camp's Population
37 Days after the Close of the Experiment

Group	Day Cultured	Number Cultured	Type I		Other Meningococci		Total Carriers		Standard Error
			Number	%	Number	%	Number	%	
Treated...	37	90	18	20.0	0	0.0	18	20.0	4.1
Untreated.	37	134	93	69.4	16	11.9	109	81.3	3.3

Criterion of Significance: 3 times sigma.

among the men previously treated, however, the carrier rate had risen to but 20.0 per cent (table 9). Carriers successfully treated with sulfadiazine became reinfected relatively slowly after the withdrawal of the drug in spite of constant exposure to the specific organism.

DISCUSSION

Sulfadiazine is apparently fully as effective as other members of the sulfonamide group in the treatment of meningococcus carriers. No positive cultures were obtained after a course of 8 grams administered over a period of 72 hours. Although there was no evidence of drug toxicity among the men treated, a smaller dose would be preferable if it were equally effective. That such may be the case is suggested by the observation that of 12 carriers given 4 grams of sulfadiazine in divided doses during 12 hours, all 12 yielded negative cultures 24 hours later. This question should be subjected to further investigation under controlled conditions.

Some possible practical applications of these results are obvious. If the entire population of the camp was treated simultaneously most, if not all, of the carriers should become negative within 72 hours, and the further spread of the epidemic halted. Emphasis must be laid upon "simultaneous treatment" since our limited experience leads us to believe that a fair proportion of former carriers cleared up by means of specific chemotherapy tends to become positive once more during the ensuing weeks if they are continually exposed to reinfection.

Mass therapy in this manner might not always be practicable because of the amount of drug required and because of the minute but ever present

danger of drug reactions.   Smaller groups of men about to leave the camp for duty elsewhere might well be subjected to such a course of chemotherapy for the twofold purpose of diminishing the chances of clinical cases occurring subsequent to their departure, and of insuring the prevention of the spread of the disease to fresh bodies of men by means of carriers.

As shown in tables 5 and 7, the carrier rate among untreated individuals varied considerably on three successive nasopharyngeal cultures taken 72 hours apart.   Only 94 (or 50.5 per cent) gave consistent results throughout, the others showing one or more changes in type, or from positive to negative, or vice versa.   One individual showed a Type II alpha on the first examination, a Type I on the second, and a Type II on the third.   Although every effort was made to use standard methods of culture, isolation and typing throughout the three examinations, it is impossible to say that the variations noted were due entirely to true biological changes rather that to unavoidable differences in technic.   Our experience bears out Branham's view [8] that a more accurate picture of the carrier state is given by several examinations of the same sample as compared to a larger group cultured but once.

SUMMARY

Sulfadiazine is effective in clearing the nasopharynx of meningococci since all of 161 meningococcus carriers receiving 8 grams of the drug over a period of 72 hours yielded negative cultures on the fourth day.   No untoward effects from the drug were noted and men so treated reacquired latent infection but slowly, in spite of constant exposure to the specific organism. Some possible practical applications of these facts are discussed.

BIBLIOGRAPHY

1. MEEHAN, J. F., and MERRILLES, C. R.: An outbreak of cerebrospinal meningitis in a foundling hospital: The treatment of carriers with M. & B. 693, Med. Jr. Australia, 1940, ii, 84.

2. FAIRBROTHER, R. W.: Cerebrospinal meningitis, the use of sulphonamide derivatives in prophylaxis, Brit. Med. Jr., 1940, ii, 859.

3. GRAY, F. C., and GEAR, J.: Sulfapyridine (M. & B. 693) as a prophylactic against cerebrospinal meningitis, South African Med. Jr., 1941, xv, 139.

4. VAN ROOYEN, C. E., and MORRIS, J. C.: Bacteriological researches on cases of cerebrospinal meningitis, convalescents and carriers, Jr. Roy. Army Med. Corps, 1941, lxxvi, 200.

5. STRONG, P. S., and BLUMBERG, J. M.: The treatment of fifty-six meningococcus carriers with chemotherapy, Mil. Surg., 1943, xcii, 59.

6. MUELLER, J. H., and HINTON, J.: Protein-free medium for primary isolation of the gonococcus and meningococcus, Proc. Soc. Exper. Biol. and Med., 1941, xlviii, 330.

7. COX, O. F., McDERMOTT, M., and MUELLER, J. H.: Delayed planting of gonococcus cultures, Ven. Dis. Inform., 1942, xxiii, 226.

8. Personal communication.

HEPATIC DAMAGE ASSOCIATED WITH SULFON-
AMIDE THERAPY IN INFANTS AND CHILDREN.
I. MORPHOLOGIC PATHOLOGY *

By Maud L. Menten, M.D., Ph.D., F.A.C.P., and Marie A. Andersch,
Ph.D., *Pittsburgh, Pennsylvania*

THE introduction of the sulfonamides into chemotherapy undoubtedly has reduced appreciably the mortality rate of many infections. However, certain untoward effects were not unexpected because of the inherent toxicity of these drugs and because of individual idiosyncrasy. A number of clinical reports have appeared regarding the deleterious effects of the sulfonamides on the hematopoietic system and the urinary tract. Toxic effects on the liver, as indicated by the development of jaundice, have been of less frequent occurrence. Varying degrees of pathologic change have been found by us in the liver of several infants and children dying during the course of sulfonamide therapy, although during life there was little evidence of jaundice. This paper deals with the liver pathologic lesions encountered.

The first recorded case of hepatic damage associated with the sulfonamides was reported in 1937 by Hagerman and Blake [1] who in discussing febrile reactions with sulfanilamide therapy cite one instance of jaundice which cleared up on discontinuance of the drug. During the following two years seven other investigators [2, 3, 4, 5, 6, 7, 8] listed 11 patients showing injurious effects on the liver from sulfonamides. Four of these patients died and in the only one in which necropsy was performed, Cline [6] found acute yellow atrophy. In 1941, Berger and Applebaum [9] observed early acute yellow atrophy following ingestion of 26.6 gm. of sulfanilamide. About the same time Tragerman and Goto [10] found both clinical and histologic evidence of liver and kidney damage in a patient in whom death had followed the administration over five days of 34 gm. of sulfanilamide for gonorrheal arthritis. Spring and·Bernstein [11] and Rothstein and Cohn [12] have recorded one and two cases respectively of toxic hepatitis following sulfathiazole. Hoyne and Larimore [13] have described cloudy swelling of the myocardium, liver and kidney in a patient who received this drug. Lederer and Rosenblatt's [14] recent observation of focal necrosis in the liver and other organs of four patients following sulfathiazole treatment·indicates that widespread pathologic change may be associated with sulfonamide therapy. Their youngest patient was 15 years of age. There have been few reports of liver damage in children associated with the sulfonamides. Carey,[15] commenting on the use of sulfanilamide and related compounds in pediatric practice, says "a few cases of hepatitis and jaundice have been observed during chemo-

therapy in infants and children." Greiner [16] has noted icterus, enlarged and tender liver, with tyrosin and leucin in the urine, following the administration of sulfapyridine to two children.

Various symptoms associated with sulfonamide therapy have been observed in this hospital. A decrease in the number of circulating leukocytes, reflected in a depression in maturation of the late myelogenous elements of the bone marrow, was most frequently encountered. A moderate number of children have shown hematuria and skin lesions, and occasionally jaundice has occurred. An increased incidence of hepatic lesions in children in whom sulfonamide therapy has been the one common factor has been observed by us in postmortem studies during the past three years. Sulfanilamide, sulfapyridine, sulfathiazole and sulfadiazine were included in the therapy. We believe that the pathologic changes in the liver are referable to the sulfonamide used.

During the three years ending April 1, 1942, 299 necropsies were performed in Children's Hospital and among this number 38 cases of definite liver disease were studied. These 38 cases were divided into three groups, depending on the severity of the pathologic changes. The first group included three patients in whom the outstanding lesion was a focal necrosis of the liver. Group II consisted of nine patients in whom definite central necrosis was the most prominent feature. The remaining 26 patients forming group III showed beginning central necrosis on a background of serous hepatitis and hepatic cellular dissociation.

Group I. The three patients comprising group I will be discussed individually. All the pathologic findings will be included, but only the hepatic lesions will be described in detail. Two patients received sulfapyridine and one received sulfathiazole.

CASE REPORTS

Case 1. C. R., a five month old, white male, was admitted to the hospital on February 20, 1939 with fever and convulsions which occurred 12 hours before admission and which had been preceded by a cold for two weeks. Pneumococcic meningitis which had its origin in a right pneumococcic mastoiditis was present.

Physical examination revealed an acutely ill child with a tense and bulging fontanelle. The pupils did not react to light and the right ear drum was dull and bulging. There was a mucopurulent nasal discharge. Moist râles were detectable through the entire chest, but there was no definite evidence of consolidation. Reflexes were normal. Kernig's sign and nuchal rigidity were absent.

Urinalysis showed 1 + albumin with occasional granular casts and white blood cells. The hemoglobin was 8.5 gm., the red blood cells 3,000,000 and the white blood cells 24,000 with 62 per cent polymorphonuclear cells. Roentgenogram of the chest showed small shadows scattered throughout both lobes. Spinal fluid was under pressure and contained 12,000 cells per cu. mm., mostly polymorphonuclears, and pneumococci, type 27. Sulfapyridine was given at three hour intervals for eight days to the amount of 17 gm. The temperature remained between 102° and 104° F. during the first week. On February 22, 1939 a bilateral myringotomy was performed. Spinal fluid on the eighth day contained 600 cells per cu mm. Sulfapyridine was discontinued for 24 hours and the temperature rose promptly to 106° F. Sulfapyridine was again

started; in the next three days 3.5 gm. were given and the temperature fell to 100° F. The spinal fluid became clear and contained only 45 polymorphonuclears per cu. mm. Sulfapyridine was again discontinued. The temperature rose to 106° F. The general condition became poor and, on March 6, 1939 deep jaundice appeared over the entire body. A whole blood transfusion of 75 c.c. was then given. The child had also received pitressin and magnesium sulfate from time to time in an attempt to relieve the abdominal distention. On March 7, 1939 the patient died.

The necropsy was performed five hours after death. The principal gross findings were a pneumococcic meningitis, bronchopneumonia, ascites, jaundice, hepatomegaly and left mastoiditis. The meninges were infiltrated with a thick purulent exudate which covered the base and lateral surfaces of the brain, which was soft and congested. The liver weighed 348 gm. and was of a brownish color, mottled with lighter areas which suggested focal necrosis.

Microscopically, besides necrosis of the liver there were in the other organs focal areas of degeneration with partial loss of myocardium, interstitial pneumonia, acute and early chronic glomerulonephritis, acute splenitis and interacinar fibrosis of pancreas.

Liver. The architectural pattern of the liver was maintained, but histology was interrupted because of necrosis of about 10 or 15 per cent of the liver cells. Throughout there was a serous hepatitis with cellular dissociation, and irregularly distributed central and focal necrosis. The picture varied in intensity in different parts of the liver. The serous hepatitis was characterized by shrinking of the liver cords with widened perisinusoidal (Disse) spaces. The cytoplasm was dense except where hydropic, fatty or granular degeneration had occurred. The Disse spaces contained a variable amount of pink granular material and an occasional red blood cell and were intersected by a loose reticular network of fine, wrinkled fibrils extending between the Kupffer and hepatic cells. The endothelial cells were somewhat hypertrophied in the vicinity of their nuclei. The sinusoids contained serum and blood cells and a moderate number of polymorphonuclear cells. Areas of beginning central necrosis showed fatty infiltration and fatty or granular degeneration progressing to necrosis and loss of cytoplasm. The majority of the nuclei took a fairly normal stain but a small percentage was pyknotic or had disappeared. There was an extensive bile stasis and many of the canaliculi were ruptured. In addition there were small patches of focal necrosis, four to six liver cords in diameter, showing cells either shrunken and deeply stained, or undergoing dissolution and having a vacuolated necrotic appearance (figure 1). Karyolysis or complete loss of nuclei was the rule in such patches. Sometimes the necrotic cells remained as masses of granular debris surrounded by a wrinkled cell membrane. There were in these focal areas many polymorphonuclear cells which sometimes appeared actually to lie within the necrotic cells. Sudan IV staining showed globules of fat in cells throughout the lobule but greatest in number in the areas of degeneration. The necrotic areas were irregular in distribution, but were most frequently seen in the midzone of the lobule. In some parts of the liver there was a coalescence of the necrotic areas with a picture approximating acute yellow atrophy. In the periportal septa the bile ducts frequently contained a pink granular material and an occasional cell. There were few if any inflammatory cells. The wall of the hepatic artery was somewhat thickened. The liver capsule was thin and fairly normal.

Brain. There was an extensive purulent meningitis with edema and degeneration of subjacent cortex. Throughout the cortex, chromatolysis and vascular collaring were seen.

Kidney. Most of the glomeruli were enlarged, but a few were contracted and contained a pinkish homogeneous material in some of the tufts. These small glomeruli, which frequently showed a thickened capsule, were found in cortical streaks

of early scar tissue associated with remnants of degenerating tubules. The vessels in these areas showed a thickened intima. The tubules and especially the proximal convoluted and ascending limb of loop of Henle showed compensatory hypertrophy. Many of the lumina contained pink granular material. There was a considerable loss in the number of collecting tubules and those remaining often contained eosinophilic granular casts.
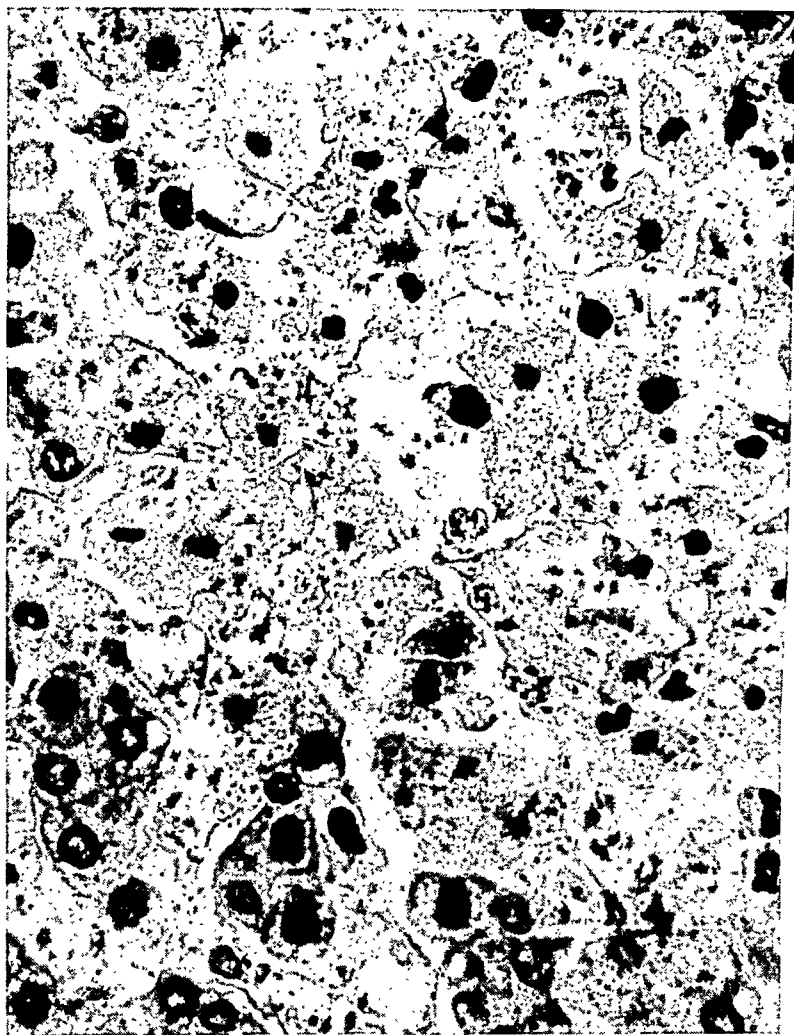
FIG. 1. Small area of early focal necrosis showing disintegration of hepatic cells and at lower left corner of section the uninvolved liver cells. × 700.

Bone Marrow. The bone marrow showed a preponderance of early myeloid cells and a paucity of polymorphonuclears.

Spleen. There was an acute splenitis with marked congestion and pigmentation.

Lung. The lung showed a patchy interstitial pneumonia, most marked around the bronchi in which there was a loss of lining epithelium in part or in whole. The intervening tissue was generally normal. The alveoli in the involved areas contained serum and a few macrophages filled with debris and pigment. The alveolar walls were thickened and contained mononuclear cells. Very few polymorphonuclears were seen in the alveoli or in their walls. No organisms were identified in Brown-Brenn preparations of lung or spleen.

Case 2. P. K. was a well developed, poorly nourished, acutely ill white male child, five months of age, admitted to the hospital on April 3, 1940 with meningitis. The anterior fontanelle was bulging and pulsating. The nasal alae were dilated and the throat was injected. There was a definite nuchal rigidity, reflexes were hyper-active, and the Kernig sign was 1 +. The extremities were rigid. There was a slight opisthotonos and a marked tenderness along the spinal column. Physical examination of chest and abdomen was negative. During the child's 39 days of hospitalization his red blood count remained about 3,000,000 per cu. mm., although 250 c.c. of whole blood were transfused over this period. The white blood count varied from 8,600 to 24,500 per cu. mm. Differential count ranged between 74 per cent and 90 per cent neutrophiles. The urinalysis showed a 1 + albumin with an occasional neutrophile. Roentgenogram of mastoid and chest were negative. Spinal fluid on admission showed 3,900 cells per cu. mm., polymorphonuclears predominating, 3 + globulin and pneumococci, type 18.

Sulfapyridine was given by mouth at three hour intervals to the amount of 7.5 gm. for the first four days and then discontinued for one and one-half days. Following this interlude, 36 gm. were given by mouth through the 17 days ending April 25, 1940. At that time only 19 white blood cells per cu. mm. were present in the spinal fluid, but the globulin was still 4 +. Culture and smears were negative. On April 19, 1940 the sulfapyridine blood level was too low to be read, and on April 24 was 3.4 mg. per cent. Another 8.5 gm. of sulfapyridine were administered between April 25 and April 30. On the latter date the spinal fluid again contained pneumococci and the cell count began to rise gradually. The dosage was then increased, and 11 gm. were given in the four day period ending May 6 with no improvement. Cells in spinal fluid then reached 1135 per cu. mm. In the next two days, May 6 and 7, in addition to oral administration, 2 gm. of the sodium salt were slowly injected subcutaneously and again on May 9 another 2 gm. of the sodium salt were given subcutaneously, but the child failed to improve. On both May 6 and May 7 the sulfapyridine blood concentration was 3 mg. per cent. Oral administration was continued and in addition on May 11, 4 gm. of the sodium salt were given intravenously. The child died on May 12, 1940, on which day the spinal fluid cell count was 380 per cu. mm. Seventy-four gm. of sulfapyridine had been given between April 3 and May 12. Sulfapyridine blood determinations showed, with the oral administration of sulfapyridine, the highest level was 3.4 mg. per 100 c.c. The level rose to 6.5 mg. after the intravenous administration of sodium sulfapyridine.

The autopsy was performed two hours after death. The chief findings were purulent meningitis and bronchopneumonia. The meninges showed a purulent exudate which was most marked in the frontoparietal regions and along the sagittal sulcus where the meninges were markedly thickened. In the exudate in many of the sulci were small isolated pockets of pus which were being walled by fibrosis. The mastoids and sectioned brain grossly appeared negative.

The liver weighed 292 gm., was slightly enlarged, congested and showed the yellow mottling of central necrosis on a dark red background.

Microscopically, besides the central necrosis, there were acute hepatitis, bronchopneumonia, and acute splenitis. Brain and liver showed the most interesting lesions.

Brain. In addition to a widespread generalized fibrosis of the meninges there were small abscesses situated in the cortical sulci where pus pockets, which had been snared off by fibrin, were being organized. In the cortex there was congestion with chromatolysis and enlarged Virchow-Robin spaces which were filled with many lymphocytes.

Lung. The lung showed an acute bronchiolitis and peribronchiolitis with an encircling patchy interstitial pneumonia. The alveolar walls were thickened because of capillary congestion; neutrophilic and round cell infiltration. Most of the bron-

chioles had lost their epithelium; their walls and lumina were infiltrated with neutrophiles. Many Gram-positive diplococci were seen in Brown-Brenn preparations.

Liver. The liver throughout showed moderate serous hepatitis, cellular dissociation and congestion. The majority of the liver cords were shrunken, the cytoplasm stained a deep pink and showed granular and fatty degeneration. The widened sinusoids contained a fair number of neutrophiles. Many small areas of beginning focal necrosis averaging four or five liver cords in diameter were seen, mostly in the midzone of the lobule. The cells in the center of these areas were shrunken, necrotic and without nuclei. The peripheral cells likewise were undergoing dissolution but the nuclei were pyknotic. Polymorphonuclear cells were beginning to collect at the edges of the foci. In other liver sections the necrotic areas occurred in groups of three or four cells and were much more diffusely distributed. In some parts of the liver coalescent necrotic areas involved at least one-third to one-half of the lobule.

Kidney. Kidneys were similar to those seen in case 1.

Spleen. The spleen showed extensive congestion, intra- and extracellular blood pigment, and very many neutrophiles. The malpighian corpuscles were reduced mainly to the germinal centers, which showed the large constituent mononuclear cells filled with such numbers of degenerating polymorphonuclears as to give the impression of small abscesses. Scattered irregularly throughout the pulp were small necrotic areas, consisting of polymorphonuclears in varying stages of degeneration on a background of large degenerating monocytic cells. We do not believe these areas are comparable to the focal necrosis seen in the liver.

Case 3. The patient, R. S., was a well developed, somewhat emaciated, eight and one-half month old, white male child, acutely ill, semiconscious and cyanotic. He was admitted on January 12, 1941 with a history of fever for 24 hours, cough of two weeks' duration and pneumonia six months previously. The respirations were rapid and there was a flaring of the alae nasi. The nose was full of thick mucus, the tonsils were enlarged, and the pharynx was reddened. There was no nuchal rigidity and the Kernig sign was positive. The mastoids were negative. Over the chest moist crackling râles were heard. Otherwise, the examination was negative except for muscular atonia.

Soon after admission the child had convulsions. The temperature varied between 102° and 106° F. During the 48 hours of hospitalization the child was given at four hour intervals by mouth a total of 8.5 gm. of sulfathiazole, with an initial dose of 0.5 gm.

On admission the hemoglobin was 10.5 gm., red blood cells 4,650,000, the white blood cells 59,800 with 50 per cent polymorphonuclears per cu. mm.

The autopsy, performed one hour after death, showed grossly edema and congestion of the brain, and confluent bronchopneumonia of upper and lower right lobes.

The liver weighed 307 gm. and was approximately normal in size.

Microscopically, the outstanding pathologic changes were limited to the lungs, liver and spleen.

Lung. In the left lung there was an early interstitial pneumonia, bronchiolar in distribution, with thickening of the alveolar walls by infiltrating neutrophiles and mononuclear cells. The alveoli contained mononuclear cells and a few polymorphonuclears.

The right lung showed a confluent bronchopneumonic involvement. The alveolar walls were somewhat thickened with neutrophiles and mononuclear cells. The alveoli contained a pink staining material and great numbers of neutrophiles. In the less involved areas there was an infiltration of monocytes and neutrophiles in the alveolar wall. The epithelium of the bronchi was desquamated and their lumina contained large numbers of polymorphonuclears. The pleura was edematous.

Liver. The general architecture of the liver appeared intact. The cellular structure seemed somewhat loose because of the moderate amount of serous hepatitis, the cellular dissociation, and scattered patches of deep reddish staining focal necrosis. The general cellular pathology was similar to that in case 1 except that there was more hypertrophy of the Kupffer cells and an increased number of round dissociated cells in the liver cords. The sinusoids were somewhat narrow and contained a considerable
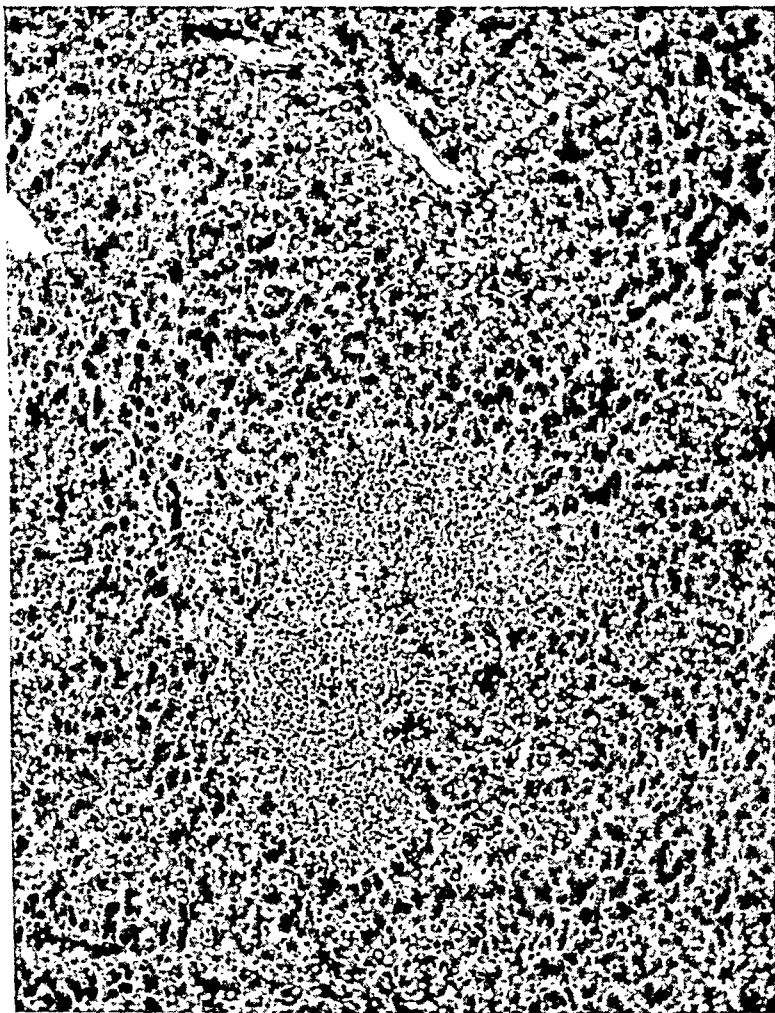
FIG. 2 (A). Section of liver showing area of focal necrosis. × 110.

amount of serous precipitate and occasional polymorphonuclears. The focal necrosis in this liver was the most pronounced of the three cases. The necrotic patches varied in size from a width of four or five to eight or ten liver cords (figures 2 A and 2 B). Their position in the lobule varied considerably and they frequently occurred at one edge of the central vein. The patches were distinguished by a dense eosinophilic staining and considerable shrinkage. Many of the cells were rounded and showed marked decrease in size with disintegration of cytoplasm and a wrinkled cell membrane. Polymorphonuclear cells were numerous in such areas and sometimes appeared to be within the necrotic cells.

Adrenal. In the adrenal the zona fasciculata and glomerulosa showed considerable granular degeneration. No definite areas of focal necrosis were seen.

Heart. The heart showed here and there fragmentation with loss of cross striation and pyknotic nuclei, and irregularly distributed nests in which two or three of the heart cells were completely disintegrated. There were no eosinophiles present and no definite areas in which distinctive focal necrosis with neutrophilic infiltration was seen.
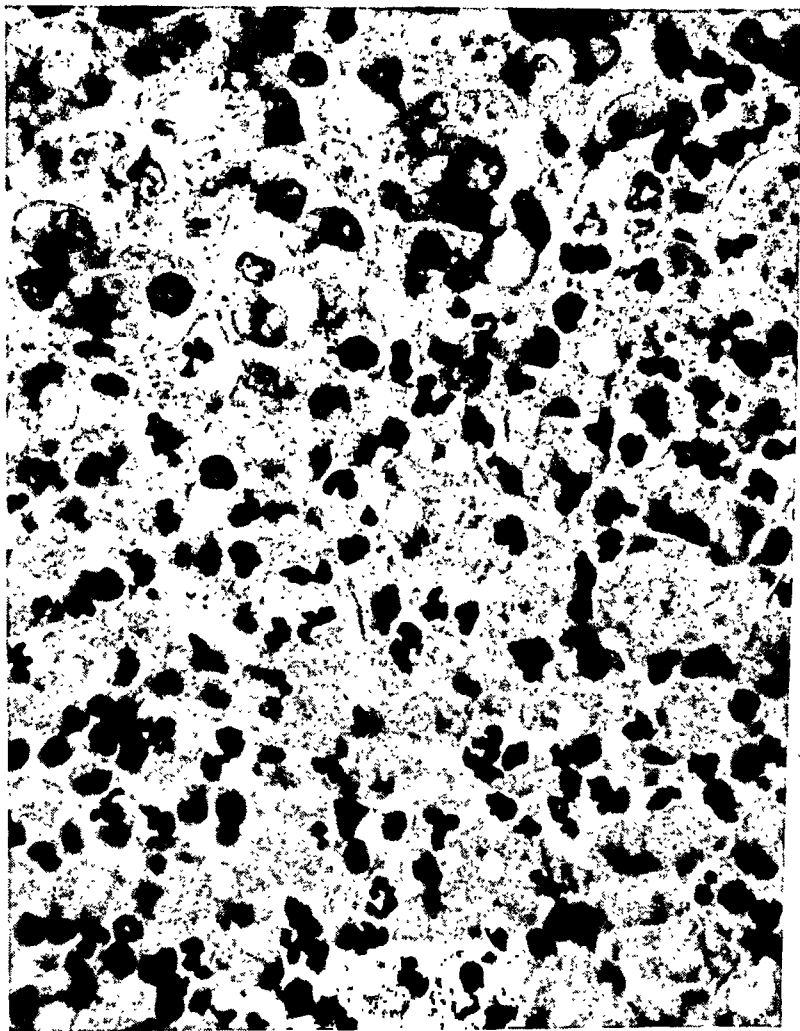
FIG. 2 (B). Showing cellular disintegration and extensive neutrophilic infiltration in the area of focal necrosis. × 700.

Lung. There was a patchy bronchopneumonia in which occurred occasional areas of focal necrosis intersected by the more resistant tissues of the alveolar walls.

Kidney. This kidney resembled the kidney in case 1 except that there was perhaps more tubular degeneration.

Spleen. There was an acute splenitis and a marked thickening of the intimal lining of the capillaries. The malpighian corpuscles were represented mainly by small germinal centers. Small areas of focal necrosis composed of degenerating reticuloendothelial cells infiltrated with neutrophiles were scattered throughout.

TABLE I

Clinical Diagnosis and Sulfonamide Dosage in Group II Characterized by Central Necrosis of Liver

Name	Color Sex	Age	Clinical Diagnosis	Days in Hospital	Sulfa-pyridine in gm.	Na Sulfa-pyridine in gm.	Sulfa-nilamide in gm.	Sulfa-thiazole in gm.	Na Sulfa-thiazole in gm.	By Mouth	Intra-spinally	Intra-venously	Duration of Therapy in Days	Postmortem Pathology Other Than Liver Lesions
T. C.	W–M	8 mo.	Pneumo. meningitis, type 7	3			2			+			3	Pneumococcic meningitis, type 7, bronchopneumonia, encephalitis, pancarditis, lumbosacral spina bifida
J. M.	W–M	10 yr.	Pneumo. meningitis, type 23	19	35					+			13	Rheumatic pancarditis, pneumococcic meningitis type 23, bilateral bronchopneumonia, chronic gastritis, hemorrhagic colitis, granular degeneration of kidney, generalized bullous dermatitis
D. R.	W–F	9 mo.	Influenzal broncho-pneumonia	23	33	2				+	+		22	Influenzal meningitis, bronchopneumonia, degeneration of thoracic and spinal cord segments, acute splenitis, granular degeneration of kidney
M. G.	W–F	30 mo.	Influenzal broncho-pneumonia	2	4					+			2	Influenzal bronchopneumonia and empyema, acute splenitis, granular degeneration of kidney
R. C.	W–M	9 yr.	Pneumo. meningitis, type 5	1.5	10	6				+		+	1.5	Pneumococcic meningitis, type 5, bronchopneumonia, granular degeneration of kidney
D. F.	W–M	7 yr.	Laryngo-tracheo-bronchitis	1		1		4.6		+		+	1	Laryngotracheobronchitis (hemolytic streptococcic, group A), acute splenitis, bronchopneumonia
P. S.	W–F	10 yr.	Broncho-pneumonia	7				7	19	+		+	7	Acute splenitis, acute interstitial nephritis, cystic dilatation of pancreas
J. M.	C–F	22 mo.	Pertussis broncho-pneumonia	2				1.6		+		+	2	Umbilical hernia, bronchopneumonia, pertussis
W. E.	W–M	3 mo.	Pneumo. meningitis	1.5	2	1.6				+		+	1	Bilateral otitis media, pericardial effusion, ascites, anasarca, dilatation of right heart, pneumococcic meningitis

Comment. The gross appearance of the liver in these three cases gave no inkling of the presence of focal necrosis and the microscopic finding was quite unexpected. This type of lesion had not been observed by us previously in any necropsy material in this hospital and appears to be related to the sulfonamide therapy.

Group II. The characteristic gross picture of central necrosis was seen to a varying extent in all nine livers of group II. In the majority of the livers studied the fine yellow mottling was seen grossly only in the outer half or two-thirds of the right lobe of the liver. This area of the liver has been demonstrated by McIndoe and Counsellor [17] and by Copher and Dick [18] as that receiving blood from the large mesenteric vein, the blood of which maintains its entity as a "stream line" in the portal vein. Thus this part of the liver receives the blood collected from the small intestines which, therefore, contains much of the absorbed orally administered sulfonamides. In three of the cases in which the drug had been injected intravenously late in the treatment, the gross distribution of central necrosis was fairly uniform throughout the liver. Pertinent data relating to the second group have been assembled in the table.

It is of interest to note that pneumococcus, either as a primary or secondary invader was a causative agent. The amount of sulfonamide administered varied widely and bore no definite relation to the extent of the lesion which microscopically ranged from a small area lying immediately around the central vein to the inner two-thirds of the lobule. All of the sections also showed extensive serous hepatitis and more or less dissociation. The dissociated cells varied from those with rounded edges, but still intact and retaining a fair staining quality, to small nests composed of two or three degenerating or necrotic cells with karyolytic nuclei, more or less detached from the contiguous cells of the liver cord.

Group III. The third and largest group of 26 patients showed liver changes consisting of serous hepatitis and a beginning central necrosis. The pathologic change was similar to group II but less in degree and more varied in distribution within different sections. As will be mentioned in the following paper, serum of one of these patients during life gave a positive reaction with the colloidal gold test for liver function. The clinical diagnosis in this group, as in group II, was mainly upper respiratory infections with pneumococci as an outstanding causative agent.

DISCUSSION

A comparison of the recorded number of necropsy cases showing central necrosis during the three years previous to the institution of sulfonamide therapy with the recorded number showing this lesion during a similar period after institution of treatment with these drugs reveals a significant increase under the sulfonamide régime. Only six such cases were encountered in the first triennium as contrasted with 15 cases in the second triennium. The six cases of the first period are made up of two blood dyscrasias with severe

anemia, two encephalitides of long standing, a diabetic coma and an osteomyelitis. The 15 cases, during the sulfonamide treatment period, include two cases of cerebral hemorrhage of the newborn, one granuloma of lung, of unknown origin, one cystic fibrosis of the pancreas with lung abscess, one rheumatic pancarditis, one leukemia and nine cases of infection. In the nine infections, pneumococcus was an outstanding infectious agent. Central necrosis of liver was negligible in these infections in the years previous to drug therapy. The logical conclusion apparently is that the increased incidence of central necrosis of the liver is referable to the added hepatotoxic action of a sulfonamide in the presence of a bacterial toxin. The observed increase in milder hepatic disease accompanying sulfonamide therapy may likewise be explained by this modus operandi. The rôle of serous hepatitis as an initial factor in the development of liver lesions has been stressed by Eppinger.[19] This edematous condition of the liver is not generally of frequent occurrence as Keschner and Klemperer [20] observed only 79 examples, and many of them were in cardiac conditions, in 505 necropsies. Only a small percentage were associated with pneumonias. The possibility that the liver of young individuals may be more vulnerable to toxins than that of adults may explain in part the high incidence of liver injury in our series. With discontinuance of the drug reparation of the damage which occurs in the milder hepatic lesions and restitutions of liver tissue undoubtedly occurs. As stated in the following paper, four cases in which abnormal liver function tests were obtained during treatment were found to be normal three months after the discontinuance of the drug. Presence of retrograde, or regenerated, tissue within the liver may underlie the phenomenon in which a second course of sulfonamide therapy, following a previous course by an interval of a few days to several weeks, leads to more rapidly developing damage than with one continuous series. Other investigators have reported such hypersusceptibility following previous sulfonamide therapy.[21, 22, 23] This type of focal necrosis has not been previously seen by us in children. The histological picture of the focal necrosis produced by sulfathiazole is identical with that described by Lederer and Rosenblatt.[14] A similar pathologic change, although of less intensity, has occurred with sulfapyridine. The development of liver damage is not in direct relation to the amount of drug used and seems to be controlled by individual idiosyncrasy of the patient or some deficiency or alteration in chemical composition of liver. It is not possible at present to say whether this lesion is due to the combined hepatotoxic action of bacterial products and a sulfonamide or only to a specific drug effect. The diversified distribution of the lesion within the lobule supports the latter explanation. Detailed examination of microscopic sections of hearts of children have not revealed the eosinophilic infiltration accompanying sulfonamide therapy described by French and Weller.[24]

Calling attention to the deleterious effect of sulfonamides is not intended to discredit or to discourage their use, but rather to urge the adoption of routine liver function tests as a means of detecting developing liver damage.

SUMMARY

1. In the 299 necropsies performed during three consecutive years in the Children's Hospital of Pittsburgh, 38 instances of liver disease associated with sulfonamide therapy were observed.

2. This pathologic change has been classified as follows. Group I, Toxic necrosis of liver in three patients; Group II, Toxic central necrosis in nine patients; Group III, Serous hepatitis and beginning toxic central necrosis in 26 patients.

3. No definite relationship could be established between the amount of sulfonamide dosage and the development of liver lesions.

BIBLIOGRAPHY

1. HAGERMAN, P. O., and BLAKE, F. G.: A febrile reaction to sulfanilamide; drug fever, Jr. Am. Med. Assoc., 1937, cix, 642–646.

2. SAPHIRSTEIN, H.: Hepatitis and toxic erythema with desquamation due to sulfanilamide, Urol. and Cutan. Rev., 1938, xxxxii, 101–102.

3. LONG, P. H.: The clinical use of sulfanilamide and its derivatives with special reference to their possible toxic effects, Jr. Ohio Med. Assoc., 1938, xxxiv, 977–981.

4. BANNICK, E. G., BROWN, A. E., and FOSTER, F. P.: Therapeutic effectiveness and toxicity of sulfanilamide and several related compounds, Jr. Am. Med. Assoc., 1938, cxi, 770–777.

5. GARVIN, CURTIS F.: Toxic hepatitis due to sulfanilamide, Jr. Am. Med. Assoc., 1938, cxi, 2283–2285.

6. CLINE, E. W.: Acute yellow atrophy of the liver following sulfanilamide medication, Jr. Am. Med. Assoc., 1938, cxi, 2384–2385.

7. FITZGIBBON, P., and SILVER, B.: Necrosis of the liver (case) following use of sulfanilamide, California and West. Med. Jr., 1939, l, 123–125.

8. LONG, P. H., BLISS, E. A., and FEINSTONE, W. H.: Mode of action and clinical use and toxic manifestations of sulfanilamide, Jr. Am. Med. Assoc., 1939, cxii, 115–121.

9. BERGER, S. S., and APPLEBAUM, H. S.: Toxic hepatitis due to sulfanilamide, Jr. Lab. and Clin. Med., 1940–1941, xxvi, 785–790.

10. TRAGERMAN, L. J., and GOTO, J. M.: Fatal reactions to administration of sulfonamide drugs, Jr. Lab. and Clin. Med., 1939–1940, xxv, 1163–1176.

11. SPRING, M., and BERNSTEIN, I.: Coexistence of toxic hepatitis, acute hemolytic anemia and renal damage following sulfanilamide therapy. Report of a case, ANN. INT. MED., 1940, xiv, 153–164.

12. ROTHSTEIN, I., and COHN, S.: Acute hemolytic anemia, auto-agglutination, toxic hepatitis and renal damage following sulfathiazole therapy, ANN. INT. MED., 1942, xvi, 152–162.

13. HOYNE, A. L., and LARIMORE, G. W.: Sulfathiazole as a cause of death, Jr. Am. Med. Assoc., 1941, cxvii, 1354.

14. LEDERER, M., and ROSENBLATT, P.: Death during sulfathiazole therapy, Jr. Am. Med. Assoc., 1942, cxix, 8–18.

15. CAREY, B. W.: Use of sulfanilamide and related compounds in diseases of infancy and childhood, Jr. Am. Med. Assoc., 1940, cxv, 924–929.

16. GREINER, K.: Toxische Leberschädigung bei der Behandlung mit Sulfapyridin, Klin. Wchnschr., 1941, xx, 97–99.

17. McINDOE, A. H., and COUNSELLOR, V. S.: Bilaterality of liver, Arch. Surg., 1925, xv, 589–612.

18. COPHER, G. H., and DICK, B.: Streamline phenomena in the portal vein and selective distribution of portal blood in the liver, Arch. Surg., 1928, xvii, 408–417.
19. EPPINGER, H.: Die Leberkrankheiten, 1937, Verlag von Julius Springer, Wien.
20. KESCHNER, H. W., and KLEMPERER, P.: Frequency and significance of hepatic edema, Arch. Path., 1936, xxii, 583–592.
21. STILES, M. H.: Hypersensitivity to small doses of sulfathiazole, Jr. Pennsylvania Med. Assoc., 1941, xxxxiv, 823–824.
22. VOLINI, I. F., LEVITT, R. O., and O'NEIL, H. B.: Cutaneous and conjunctival manifestations of sulfathiazole intoxication, Jr. Am. Med. Assoc., 1941, cxvi, 938–940.
23. LYONS, R. H., and BALBEROR, H.: Febrile reactions accompanying the readministration of sulfathiazole, Jr. Am. Med. Assoc., 1942, cxviii, 955–958.
24. FRENCH, A. J., and WELLER, C. V.: Interstitial myocarditis following clinical and experimental use of sulfonamide drugs, Am. Jr. Path., 1942, xviii, 109–122.

HEPATIC DAMAGE ASSOCIATED WITH SULFON-AMIDE THERAPY IN INFANTS AND CHILDREN. II. CHANGES IN LIVER FUNCTION TEST DURING SULFONAMIDE THERAPY *

By Marie A. Andersch, Ph.D., *Pittsburgh, Pennsylvania*

Sulfonamides have proved effective in the treatment of many infections, and in only a few instances have there been reports of clinical signs of liver dysfunction. This, however, may occasionally occur. The evidence offered in the previous paper of liver disease at times associated with sulfonamide therapy in children led to an investigation of the possibility of the early detection of hepatic damage during treatment. Liver function tests based on alteration of plasma globulin appear to be exceedingly sensitive, and with the use of one of these tests it has been possible to detect changes in liver which occurred during treatment with sulfathiazole or sulfadiazine.

There have been only a few reports in the literature in which liver function has been followed before and during therapy. DeBonis [1] found a decrease in hepatic function in five of 11 normal adults who received 0.03 gr. of sulfanilamide per kilo for three days. Watson and Spink [2] have shown that the administration of sulfanilamide to adults in usual therapeutic amounts causes acceleration of hemoglobin metabolism, and in some of these individuals an elevation of serum bilirubin was noted. Cole and Harned [3] found that the toxicity of sulfapyridine for rats was increased by a vitamin B deficient diet.

METHODS

The functional liver test of Gray [4] was used, which is based upon the fact that colloidal gold is precipitated by the diluted serum from a patient with hepatic disease but not by normal serum. According to Gray this reaction is quite specific for hepatic disease. Eighty-eight out of 96 gave positive reactions, whereas eight gave negative reactions. These eight patients included six with carcinoma of the liver. In addition to being sensitive and reliable if well controlled,[5] this test does not require intravenous injections, solutions by mouth, or the collection of quantitative urine specimens. The original method of dilution was modified so that the test could be made on smaller quantities of serum than previously used. The blood was drawn from a finger puncture by capillarity into a 2 mm. bore glass tube. The opposite end of the tube was sealed in a flame and the tube centrifuged. It was then broken at the line of demarcation of cells and serum, the serum drawn into a 20 cu. mm. hemoglobin pipette and washed into 7 c.c. of 0.9 per cent saline. This gave an initial dilution of 1 to 350, which was further

diluted to 1 : 3500, 1 : 7000 and 1 : 14000 as described by Gray. Five c.c. of acidified colloidal gold were added to 1 c.c. of each of these three dilutions and the tubes read the next day according to the usual system for the Lange reaction, viz.: red—0, red-blue—1, orchid—2, blue—3, light blue—4, and colorless (complete precipitation)—5. The colloidal gold was freshly prepared every three weeks, the acid requirement determined, and the gold reagent run against a series of negative control sera. The negative sera did not give readings higher than 332. Positive liver damage was indicated by complete precipitation in at least one tube. Some readings fell between the negative and the definitely positive groups and were interpreted as indicating early damage which might have become more marked if therapy had been continued.

The testing of the serum was begun before or during the first few days of therapy at which time the serum gave a negative reaction. The testing was repeated at approximately three day intervals until the determination showed altered liver function or until the drug was discontinued.

Complete blood counts were done on admission and from time to time in order to check any possible deleterious effect of the sulfonamides on the hemopoietic system. Hemoglobin was determined on the Fisher electro-hemometer and red cell, white cell and differential counts were made in the usual manner.

The serum concentration of sulfonamides was determined by the method of Bratten and Marshall.[6] Serum levels of drug have not been made routinely in this hospital because it has been found that the levels remain within limits on comparable therapeutic doses and usually do not exceed 7.0 mg. per cent.

RESULTS

One hundred and six patients were tested. Seventy-three of these children with initial negative readings were tested periodically during treatment with sulfathiazole or sulfadiazine. Twenty-four of these patients developed either slight or markedly positive readings in from three to 23 days. These results are tabulated in table 1 together with the type of therapy given. Of the 11 children who gave the more positive findings (table 1, part a) seven had pneumonia whereas the other four had otitis media, diphtheria, tuberculous bronchopneumonia and retropharyngeal abscess respectively. Four of these children returned to the hospital in from two to three months and were retested. It is interesting that all four had negative reactions, thus demonstrating the capacity of the liver to repair. Thirteen patients (table 1, part b) showed slight changes in the colloidal gold reaction. The probability that these changes are indicative of early liver damage is evidenced by the necropsy findings in one fatal case in this group. Death was due to influenzal meningitis and followed 15 days of treatment with sulfadiazine. This patient was included in the previous paper in group III which was characterized by a beginning central necrosis on a background of hepatic cellular

TABLE I

Data on Patients Developing Positive Colloidal Gold Reaction of Serum during Therapy

No. of Patients	Clinical Diagnosis	Age	Sulfadiazine in gr.	Sulfathiazole in gr.	Therapy in Days	Colloidal Gold Reaction	
						Initial	Final
			(a)				
7	Broncho-pneumonia	7 Mo.[1]	28		6	332	543
		8 Mo.[1]		40	3	322	532
		7 Mo.[1]	90		8	322	533
		5 Mo.[1]	97		3	322	454
		12 Mo.[1]	160		10	322	522
		6 Mo.[1]	165	168	23	222	554
		4 Yr.	390		6	322	532
1	Acute otitis media	2.5 Yr.	754		23	222	544
1	Diphtheria	11 Yr.	707		10	322	554
1	Tuberculous pneumonia	8 Mo.	243		17	332	533
1	Retropharyngeal abscess	7 Mo.		92	14	322	542
			(b)				
7	Broncho-pneumonia	3–30 Mo.	(5) 67–331		6–11	332–322	422–433
				(2) 111–225	4–7	322	
1	Lobar pneumonia	8 Yr.	450		7	322	432
1	Influenzal meningitis	1 Yr.[2]	1121		15	322	422
1	Scarlet fever	10 Yr.[2]	538		11	322	433
1	Pertussis	30 Mo.	277		11	222	422
1	Pharyngitis	4 Yr.	389		12	322	422
1	Otitis media	10 Mo.	68		3	332	433

[1] Reaction had returned to normal within three months.
[2] Necropsy.

dissociation. It is also significant for the evaluation of this liver function test that the serum from many children passed from a negative test through gradually increasing degrees of positivity to reach a final markedly positive reaction. A concrete case exemplifies this. The initial reaction of the serum

from one child was 222; the reactions in five, 17 and 33 days were 422, 533 and 543 respectively. It would seem that there were progressive changes in the serum globulin which caused progressive increases in the precipitation of the gold reagent.

There were no significant changes in the hemoglobin or in the red cell, white cell and differential counts.

Data on the 49 children who showed no alteration in colloidal gold reaction of serum during therapy are tabulated in table 2. Forty-one of

TABLE II

Cases Showing Normal Colloidal Gold Tests during Treatment with
Sulfathiazole and Sulfadiazine

Total No. of Patients	Clinical Diagnosis	Age	No. of Patients	Therapy		
				Sulfadiazine in gr. (Range)	Sulfathiazole in gr. (Range)	Duration in Days
27	Bronchopneumonia	2–24 Mo.	15	75–223		3–9
			7		131–300	3–8
			5	23–148	57–148	7–13
10	Bronchopneumonia Otitis media	4–21 Mo.	9	71–285		
			1		96	4
1	Bronchopneumonia Empyema	9 Mo.	1	55	312	15
4	Tracheobronchitis	9–18 Mo.	3	140–231		4–10
			1		102	3
2	Meningococcic meningitis	5–8 Mo.	2	231–714		7–12
2	Influenzal meningitis	2 Yr.	1	621		42
		3 Mo.[1]	1		113	8
3	Lobar pneumonia	6 Mo.–13 Yr.	3	100–315		7–10

[1] Necropsy.

these patients had pneumonia, four meningitis, and four tracheobronchitis. One child died from influenzal meningitis and necropsy was performed. The changes in the liver were not marked. They consisted of some granular degeneration of the cells and a moderate serous hepatitis. The changes were similar to those found in two cases of influenzal meningitis which had not received sulfonamides before death.

Single determinations were done on a group of positive and negative control sera and on a number of sera obtained from patients with various diseases in order to compare the type of reaction obtained. These have been included in table 3. One child in this group deserves special comment. She

was admitted with a history of anemia of long duration with a decrease in the number of myelogenous cells and a large number of nucleated reds. The tentative diagnosis was lymphatic leukemia. She was given sulfonamides for a throat infection, and the colloidal gold reaction of the serum changed from negative through a slight positive to a marked positive reaction in three weeks. This case was not included in the first table because it was thought that the blood dyscrasia per se might have influenced the colloidal gold reaction. The child died five weeks after admission, and examination of the liver showed a serous hepatitis with a beginning central necrosis, fatty and

TABLE III

Single Determinations on Positive and Negative Controls, and on Miscellaneous Patients

Number	Clinical Diagnosis	Colloidal Gold Reading	Notes
1	Toxic hepatitis	555	Icterus index 25; cholesterol 300 mg. per cent; esters 47 per cent
1	Toxic hepatitis	544	Cholesterol 60 mg. per cent; esters 10 per cent
1	Congenital obstruction of bile ducts	555	Direct van den Bergh; icteric index 75
1	Vitamin K deficiency	555	
1	Congenital syphilis	222	
1	Lymphatic leukemia [1]	543	Liver showed serous hepatitis, mild central necrosis, extramedullary hematopoiesis
1	Nephrosis	333	
1	Biliary cirrhosis [1]	555	Liver showed advanced biliary cirrhosis
25	Negative controls	322, 222	

[1] Necropsy.

granular degeneration and a diffuse infiltration of lymphocytic cells throughout the liver. These lesions were sufficiently extensive to cause alteration in the serum globulin and therefore the markedly positive colloidal gold reaction.

It would have been desirable to test the colloidal gold reaction of blood serum of a larger number of patients who did not receive sulfonamides in order to compare the effect of infection per se on liver function. This type of control patients was not available, however, because of the general use of sulfonamide therapy by the clinicians in the wards.

Discussion

Marked positive tests for altered liver function were obtained in 13 per cent of the children studied. A slightly positive reaction was obtained in an

additional 20 per cent. This latter reaction was interpreted as indicating a mild liver damage. This interpretation was borne out by the necropsy findings in one of these latter cases which showed the basic liver lesion characterizing the third group which has been described in the previous paper.

No correlation could be found between the amount or duration of the therapy and the change in the colloidal gold reaction. One child developed a positive reaction after 28 gr. of sulfadiazine were given over a period of six days whereas another maintained a negative reaction for six weeks during which time 621 gr. of this drug were administered. It would appear that besides the inherent toxicity of the drug, the vulnerability of the liver to a toxin must vary with the individual. It may be significant that the child who developed the positive reaction following only 28 gr. of sulfadiazine had received 48 gr. of sulfathiazole one month before the sulfadiazine was started. Clinical evidence in this hospital substantiates the evidence presented by other investigators that sulfonamides may at times produce a sensitivity so that succeeding small doses given a few days to a few weeks after the initial series will cause toxic symptoms.[7]

Studies on experimental animals have shown that it is difficult to induce necrosis of the liver by toxins unless the chemical composition of the liver has been previously altered. Low carbohydrate and high fat content of the liver, inadequate protein and vitamin B intake have been implicated in the increased vulnerability of the liver to hepatotoxins.[8, 9, 10, 11] If this can be shown to hold true for the sulfonamides, low liver glycogen might be a significant factor in infants and children whose small glycogen stores may be rapidly depleted by lack of food, by increased metabolism associated with fever, or by a combination of these factors. The ketosis, associated with abnormal levulose tolerance curves, which develops frequently during infections of the upper respiratory tract in children,[12] gives evidence for the rapid depletion of available carbohydrate in the younger individuals. It is also apparent that the available protein and vitamin B may be diminished during infections so that their deficiency must likewise be considered. It has been shown that rats are less susceptible to the general toxic effects of sulfanilamide when they have been previously fed on a high protein diet,[13] and another study on rats has shown that the toxicity of sulfapyridine was enhanced by a vitamin B deficient diet.[3]

It would appear desirable to determine the rôle of inadequate nutrition as a factor in the vulnerability of the liver to sulfonamides before finally evaluating the deleterious effects of these drugs.

SUMMARY

1. Gray's colloidal gold test for liver function was run on the sera of 106 patients. The serum of 73 children was tested periodically during sulfonamide therapy and single determinations were run on the remaining 33 patients for purposes of comparison and control.

2. Twenty-four of the 73 children developed positive colloidal gold reaction during therapy; eleven of these showed markedly positive and 13 slightly positive reactions. The sera of 49 children showed no change in reaction during therapy.

3. Changes in liver function reaction could not be directly correlated with the amount or duration of therapy.

4. The type of reaction obtained in four patients is discussed in relation to necropsy findings.

BIBLIOGRAPHY

1. DeBonis, G.: Toxicity of sulfanilamide for liver, Athena, 1940, ix, 225; Abstr. Jr. Am. Med. Assoc., 1940, cxv, 1928.

2. Watson, C. J., and Spink, W. W.: Effect of sulfanilamide and sulfapyridine on hemoglobin, Arch. Int. Med., 1940, lxv, 825–846.

3. Cole, V. V., and Harned, B. K.: The effects of a diet deficient in vitamin B on the toxicity of sulfapyridine, Federation Proc., 1942, i, 147.

4. Gray, S. J.: The colloidal gold reaction of blood serum in diseases of the liver, Arch. Int. Med., 1940, lxv, 524–544.

5. Mateer, J. G., Baltz, J. J., Marion, D. F., and Holland, R. A.: A comparative evaluation of the newer liver function tests, Am. Jr. Digest. Dis., 1942, ix, 13–29.

6. Bratten, A. C., and Marshall, E. K.: A coupling component for sulfanilamide determination, Jr. Biol. Chem., 1939, cxxviii, 537–550.

7. Stiles, M. H.: Hypersensitivity to small doses of sulfathiazole, Jr. Pennsylvania Med. Assoc., 1941, xxxxiv, 823–824.

8. Ravdin, I. S.: The protection of the liver from injury, Surg., 1940, viii, 204–211.

9. Messinger, W. J., and Hawkins, W. B.: Arsphenamine liver injury modified by diet, Am. Jr. Med. Sci., 1940, cic, 216–225.

10. Davis, N. C., and Whipple, G. H.: The influence of fasting and various diets on the liver injury effected by chloroform anesthesia, Arch. Int. Med., 1919, xxiii, 612–635.

11. Miller, L. L., and Whipple, G. H.: Chloroform injury increases as protein stores decrease, Am. Jr. Med. Sci., 1940, cic, 204–216.

12. Tallermann, K. H.: Ketosis accompanying infections in children, Am. Jr. Dis. Child., 1925, xxx, 476–482.

13. Kapnick, I., Lyons, C., and Stewart, J. D.: Influence of diet on sulfanilamide toxicity, Jr. Pharmacol. and Exper. Therap., 1942, lxxiv, 284–289.

THE VALUE OF THE EXAMINATION OF GASTRIC CONTENTS FOR TUBERCLE BACILLI *

By JOHN A. FOLEY, M.D., F.A.C.P., and JOHN B. ANDOSCA, M.D.,
Boston, Massachusetts

THE importance of sputum examination for tubercle bacilli in pulmonary tuberculosis cannot be overemphasized. The finding of tubercle bacilli. in the sputum establishes the diagnosis beyond all shadow of doubt. We are convinced of the necessity of gastric lavage for the detection of tubercle bacilli in these cases in which a positive sputum cannot be obtained by the ordinary method.

This method of detecting tubercle bacilli is said to have been described by Meunier [5] in 1898. He showed, in children suffering from pulmonary tuberculosis in whom sputum could not be obtained, that by means of gastric lavage 80 per cent were found to be positive. Armand-Delille and Vibert,[1] in 1927, examined the stomach lavage in 110 children suspected of pulmonary tuberculosis and found 34 positive cases. Clausen,[3] in 1931, examined the material obtained by gastric lavage from 38 adults with pulmonary tuberculosis in whom he had not been able to find tubercle bacilli by the usual method. Twenty were found to be discharging tubercle bacilli. Poulsen,[6] in 1931, claimed that in his series of cases, in spite of negative roentgenograms he was still able to make a diagnosis of pulmonary tuberculosis by demonstrating tubercle bacilli in the gastric contents. He claims the reason for a negative roentgenogram, negative clinical examination and a positive gastric lavage, is that there may be cavities which are so small that they cannot be detected by roentgenograms nor produce clinical symptoms, yet owing to their anatomical placement, are emptying infected material which after being swallowed by the patient can be detected in the stomach contents. Ulmar and Ornstein,[9] in 1933, quite ingeniously showed how tuberculous patients with negative sputa inadvertently swallowed their sputum. Following the injection of iodized poppy-seed oil into the bronchial tree by means of the bronchoscope, a roentgenogram demonstrated the presence of the entire amount of oil in the stomach. The mechanism of bronchial peristalsis accounts for the bronchial contents being raised to the level of the larynx and swallowed without the mechanism of cough. In a series of 287 cases in which there were repeated negative sputum examinations, approximately 20 per cent yielded tubercle bacilli on examination of the gastric contents. Stadnichenko and Cohen,[7] in 1936, in a series of 600 cases reported a positive finding in 30 per cent by means of gastric lavage. In 1938

Gullbring and Levin [4] demonstrated tubercle bacilli by gastric examination in 34 out of 105 cases.

During the past four years, in a series of 639 cases in whom tubercle bacilli could not be obtained either in preparations stained directly or by concentration methods, 187 patients or 29.2 per cent were found to have a positive sputum by means of gastric lavage. Thirty-two non-tuberculous cases sent mistakenly to the sanatorium were used as controls; none of these cases yielded a positive result. We believe that because of its reliability and definiteness we are justified in its use in any case suspected of pulmonary tuberculosis. Gastric lavage, apart from its diagnostic value, is of therapeutic importance when it is necessary to decide whether active treatment, such as collapse therapy, should be started. This test is helpful also as a prognostic sign to evaluate the effect of pneumothorax treatment and when it should be discontinued. The determination of when to discontinue pneumothorax is always a serious problem even for the most experienced. Gastric lavage should be done before any case of pneumothorax is discontinued. The test is of importance in deciding as to further surgical treatment. It helps to expose simulators, either those who deliberately deny that they have sputum or those who hand in false sputa for examination. The discharge group from a sanatorium is particularly interesting for it presents, so to speak, a special problem. Here is found a group of cases which, owing to their freedom from tubercle bacilli by ordinary examination, their innocent clinical picture and roentgenogram, have been termed arrested cases. It is safe to assume that a fairly good number of these cases show a positive sputum on gastric lavage. We should adhere to the principle that tuberculous lesions of the lung should not be considered healed until tubercle bacilli are repeatedly absent in the gastric contents. This would result in fewer breakdowns and readmissions to sanatoria. Burckhardt [2] invariably gives an unfavorable prognosis in cases in which tubercle bacilli are found in the gastric contents in the presence of a negative sputum unless the gastric examination becomes negative under collapse or other therapy.

The gastric contents are obtained in the early morning before the ingestion of any food in order to avoid dilution by food and gastric secretion. A Levine tube is passed nasally into the stomach, and with a Luer syringe, 30 to 50 c.c. of the concentrated gastric contents are aspirated for examination for tubercle bacilli. It is our opinion that a specimen obtained by this method gives a higher percentage of positive results than diluted contents obtained by the older method. We employ the method as recommended by J. H. Hanks for concentration of the gastric contents.

Technic. The following reagents are used: (1) digestor—1 per cent sodium hydroxide containing 0.2 per cent potassium alum and .002 per cent bromthymol blue; (2) hydrochloric acid approximately 2.5 N. (25 per cent conc. HCl by volume); (3) ferric chloride solution (1 per cent $FeCl_3$ in distilled water). The concentration is carried out by mixing 5 c.c. of the

gastric content with an equal volume of digestor and this is digested in a water bath at 37° C. for 30 minutes with occasional shaking.   2.5 N. HCl is added drop by drop with shaking until the color of the indicator denotes approximate neutrality.   Shake for 30 seconds and if flocculation does not occur in less than five minutes, add 0.2 c.c. of ferric chloride solution and shake again.   Centrifuge flocculated sample for five minutes at top speed to pack precipitate and discard supernatant fluid.   Prepare uniform smears on glass slides, dry in air, fix by heat and stain by Ziehl-Neelsen's method.

This procedure involves the incorporation of alum in the NaOH used for digesting the gastric samples.   When the specimen is neutralized the alum flocculates and collects the tubercle bacilli.   This method is simple and possesses the following advantages: 1. It reduces centrifugation time to five minutes or, if filtration through paper is desired, dispenses with centrifugation.   2. It permits preparation of uniform slides, facilitating microscopic examination.   3. It collects bacilli more completely so that a unit amount of sediment contains three to seven times more bacilli than can be collected by direct centrifugation of the same sample.   Furthermore, the flocculated precipitates do not interfere with cultivation of tubercle bacilli when small numbers are present.

The utmost care in preparation of the gastric tubes is essential in order to prevent false positive reports.   Consequently, we have used the following procedure.   The tubes are thoroughly washed with hot water and soap, and are then attached to a special water tap and water is run through them for 30 minutes.   Next the tubes are boiled for 30 minutes in a weak solution of sodium carbonate, and finally they are placed on ice overnight.

We are in agreement with other workers on this subject that guinea pig inoculation of the gastric contents is a much more delicate test and yields a higher percentage of positive results than does direct microscopy.   Stiehm,[8] in 1939, in a series of 50 minimal cases whose sputum was negative, found that 18 per cent were positive on microscopic examination of the gastric contents and 72 per cent positive on guinea pig inoculation.   In a series of 60 cases we found that 25 per cent were positive by direct smear of the gastric contents and 65 per cent positive by guinea pig inoculation.

The following table summarizes the results of the examination of gastric contents of patients with pulmonary tuberculosis as reported by different workers:

Author	Date	Cases	Per Cent Positive
Armand-Delille	1927	110	51
Clausen	1931	53	41
Poulsen	1931	15	80
Ulmar-Ornstein	1933	287	20
Stadnichenko-Cohen	1936	600	30
Gullbring-Levin	1937	105	32
Stiehm	1939	50	72

The following case reports illustrate the importance of gastric lavage in diagnosis in some cases of pulmonary tuberculosis which present a minimum of physical signs and roentgenographic findings:

CASE REPORTS

Case 1. G. O., 23 year old married housewife.

Family History: Mother and grandmother had pulmonary tuberculosis.

Past History: Pneumonia at the age of 13. This patient was admitted with a six weeks' history of weakness, fatigue, loss of appetite and loss of 11 pounds in weight, the present weight being 98 pounds. The temperature ranged from 97 to 98.4° F., pulse 70 to 100, respirations 18 to 24. The sputum was persistently negative on direct smear, but on gastric lavage tubercle bacilli were obtained. The urine was normal, and Hinton test was negative; blood picture was normal. Sedimentation rate was 18 D. L. Examination of the chest revealed moderate dullness over the right apex. The left lung was negative.

Case 2. H. R., 26 year old married nurse.

Family History: Two uncles died of pulmonary tuberculosis. Past history was negative. This patient was admitted with a four months' history of weakness and fatigue, weight loss of four pounds, present weight being 93 pounds. The temperature ranged from 97 to 99° F., pulse 80 to 110, respirations 18 to 22. The sputum was negative on direct smear, but tubercle bacilli were obtained in the gastric contents. The urine was normal and Hinton test negative; the blood picture was normal. Sedimentation rate was 11 D. L. Examination of the chest revealed slight dullness over the left apex. The right chest was negative.

Case 3. K. W., 25 year old housewife. Family history and past history were negative. This patient was admitted with a five weeks' history of dry cough, weakness, fatigue, right-sided chest pains, loss of appetite and loss of 14 pounds in weight, present weight being 118 pounds. The temperature ranged from 97 to 98.8° F., pulse 72 to 100, respirations 18 to 20. The sputum was negative on direct smear but gastric contents showed the presence of tubercle bacilli. The urine was normal and Hinton test negative; blood picture was normal; sedimentation rate was 12 D. L. Examination of the chest revealed dullness over the right base, diminished breath sounds, and a few crepitant râles. The left lung was negative.

Case 4. M. M., 19 year old student nurse. Family history: Negative. Past history: Pneumonia three times at ages of 8, 10, and 14. This patient was admitted with a four weeks' history of slight cough, fatigue and weakness. There had been no weight loss, present weight being 198 pounds. The temperature ranged from 97 to 99° F., pulse 80 to 96, respirations 18 to 20. The sputum was negative on direct smear and on microscopic examination of the gastric contents, but guinea pig inoculation of the gastric contents was positive. The urine was normal and Hinton test negative; blood picture was normal; sedimentation rate was 18 D. L. Examination of the chest revealed slight dullness over the right apex. The left chest was negative.

Case 5. E. B., 40 year old painter. Family history: Wife died of pulmonary tuberculosis. Past history was negative. This patient was admitted with a four months' history of cough, slight expectoration, streaking on three occasions, pains in right chest, weakness, fatigue, loss of appetite and loss of 21 pounds in weight, present weight being 133 pounds. The temperature ranged from 97.6 to 99° F., pulse 70 to 94, respirations 18 to 24. The sputum was consistently negative on direct smear, but examination of the gastric contents revealed the presence of tubercle bacilli. The urine was normal and Hinton test negative; the blood picture was normal; and the sedimentation rate was 9 H. L. Examination of the chest revealed moderate dullness over the right mid-lung field with a few medium râles. The left chest was negative.

Case 6. E. M., 25 year old male librarian. Family history and past history were negative. This patient was working and well when he was called to appear for examination at the Army induction center. A routine roentgenogram revealed evidence of pulmonary tuberculosis, and he was advised to enter the Sanatorium. On admission the patient was asymptomatic. Temperature ranged from 97.2 to 98.6° F., pulse 74 to 86, respirations 20 to 24. The sputum was persistently negative on ordinary examination but gastric lavage revealed tubercle bacilli. The urine was normal and Hinton test negative; the blood picture was normal; and the sedimentation rate was 10 H. L. Examination of the chest revealed slight dullness over the left apex with bronchial breathing and fine râles. The right chest was negative.

SUMMARY

1. The importance of gastric lavage for the detection of tubercle bacilli cannot be overestimated.

2. Out of 639 cases with negative sputum, 187 or 29.2 per cent were found to be positive by gastric lavage; 32 non-tuberculous cases employed as controls were all negative.

3. Guinea pig inoculation of the gastric contents definitely gives a higher percentage of positive results than direct microscopy.

4. Gastric lavage is an aid not only in establishing a diagnosis of pulmonary tuberculosis but also in its differential diagnosis, treatment and prognosis. It is in addition an accurate gauge of the infectiousness of a patient and helps to determine his relationship to society.

5. We have attempted to show by case reports the reliability and importance of gastric lavage.

We wish to express our appreciation to the Staff and the Laboratory Department.

BIBLIOGRAPHY

1. ARMAND-DELILLE, P., and VIBERT, J.: Le diagnostic bacteriologique de la tuberculose pulmonaire des jeunes enfants par l'examen du contenu gastrique, Presse méd., 1927, xxxv, 402.
2. BURCKHARDT, J.: Ueber fakultativ offene Lungentuberkulose, Schweiz. med. Wchnschr., 1941, lxxi, 604.
3. CLAUSEN, V.: Demonstration of tubercle bacilli in gastric lavage, Acta tuberc. Skandin., 1931, v, 379.
4. GULLBRING, A., and LEVIN, N.: The importance of gastric lavage for the demonstration of tubercle bacilli in adults, Acta med. Skandin., 1937, xciii, 168.
5. MEUNIER, H.: Bacilloscopie des crachats extraits de l'estomac pour le diagnostic de la tuberculose pulmonaire, Presse méd., 1898, vi, 81.
6. POULSEN, V.: Pulmonary tuberculosis in children and the demonstration of tubercle bacilli in gastric lavage, Am. Jr. Dis. Child., 1931, xli, 783.
7. STADNICHENKO, A., and COHEN, S.: Gastric lavage as means of demonstrating tubercle bacilli in pulmonary tuberculosis, Trans. of the 33rd annual meeting of the Nat. Tuberc. Assoc., 1937, xxxiii, 125.
8. STIEHM, R. H.: A review of a five year tuberculosis program among University of Wisconsin students, Am. Jr. Med. Sci., 1939, cxcvii, 517.
9. ULMAR, D., and ORNSTEIN, G.: Gastric examination in pulmonary tuberculosis with negative sputum, Jr. Am. Med. Assoc., 1933, ci, 835.

EMBOLISM AND THROMBOSIS OF THE POPLITEAL ARTERY—DIAGNOSIS AND TREATMENT *

By Joseph C. Doane, M.D., F.A.C.P., *Philadelphia, Pennsylvania*

THE basis of this report will be the presentation of a series of rather typical cases in which occlusion by embolism or thrombosis of the popliteal artery had taken place. Of the 11 cases presented, eight were from the service of the writer and the remaining three were from those of his colleagues. In these 11 patients obstruction of the popliteal had occurred 14 times.

Thrombosis and embolism of the popliteal artery are among the commoner arterial accidents. McKechnie and Allen,[1] in analyzing 100 cases of arterial obstruction found that the popliteal was embolized and/or thrombosed in 44 per cent and the femoral in 37 per cent of these cases. Embolism occurred more frequently in this series than thrombosis, although once the former takes place both proximal and distal thrombosis soon transpire.

Although the symptom picture which develops when an artery is occluded presents rather constant features, there are several factors which determine the outcome of the accident. These are the location and size of the vessel occluded, the speed with which this is accomplished, the time which elapses between the occlusion and the institution of treatment, and the degree of arteriosclerosis present in the obstructed vessel and its collateral channels. An arteriosclerotic closure of a vessel which develops slowly over a period of years is much less likely to produce a massive loss of tissue than a rapid occlusion by an embolus. In Seifert's experience,[2] sudden obstruction of the popliteal artery resulted in gangrene in about 45 per cent of the cases. Because advanced atheroma is likely to be present in popliteal thrombosis and because this accident often occurs in arteriosclerotics more or less advanced in years, gangrene of some degree occurs in a greater percentage of patients in primary thrombosis than in embolism. It appears, however, that embolism tends toward a more extensive loss of tissue than does thrombosis. It is believed that the vascular spasm which is greatest in embolic obstruction is of even greater immediate danger to the patient than the embolus itself. Thomas Lewis [3] does not concur in this belief, concluding that an embolus is too soft in consistency to produce by its impact so marked an effect on the vessel's caliber, and thus account for the early pain experienced. Seifert,[2] however, observed marked vascular spasm while performing an embolectomy. Gossett, Bertrand and Patel [4] believe that an embolus is fixed by this arterial spasm, its distal progress being thus prevented. The establishment of col-

lateral circulation must depend upon the ability of vessels to dilate so that their blood carrying capacity is multiplied or indeed upon the opening of channels not in every day use.   This dilatation is probably due to the action of a histamine-like metabolite caused by tissue ischemia rather than by the vis-a-tergo of the occluded blood stream alone.   It is sometimes almost impossible to decide whether the obstruction is embolic or thrombotic.   To attempt so to do is important, however, for emboli may be surgically removed while thrombi do not offer such good operative prognoses.

As stasis follows embolism or thrombosis, a distal as well as a proximal clot quickly forms.   It is for this reason that diagnosis must be prompt in order to avoid gross intimal damage and the formation of extensive thromboses which prevent the restoration of circulation even though an embolectomy is later performed.   This critical period must not exceed six hours and preferably should not be greater than four hours.

In popliteal obstruction, as in arterial occlusion generally, heart disease and vascular atherosclerosis are basically responsible in about 45 and 30 per cent respectively, of all cases.   Hindmarsh and Sandberg[5] found that 77 per cent of 45 patients upon whom embolectomies were performed suffered with heart disease.   Mitral stenosis with or without auricular fibrillation, myocardial disease and acute infection of the heart valves are the most frequent causes of intracardial clots.   Indeed, in approximately 30 per cent of all cases of mitral stenosis coming to autopsy, cardiac thrombosis has taken place.   When cardiac irregularities, particularly auricular fibrillation, are present, embolism is more likely.   Myocardial infarction with a resultant mural thrombosis is probably the source of the largest emboli and is not infrequently the forerunner of obstruction of the aorta, femoral or the popliteal arteries at their bifurcations.   De Takats[6] wisely warns against indiscriminate digitalization in coronary occlusion as favoring the discharge of large mural thrombi.   In subacute bacterial endocarditis emboli are usually so small that they are incapable of obstructing a large vessel since an embolus only ceases forward movement when its diameter exceeds that of a distal vessel or when it impinges on its central bifurcation point.   Emboli of medium size are apparently not uncommon, i.e., too small to obstruct the aorta, iliac or femoral, yet too large to pass on into the tibials.

The diagnosis of popliteal embolism ought not to present great difficulties. Early recognition of the existence of an arterial obstruction is highly important.   Every obstruction of a larger artery represents an emergency no less urgent than the presence of a gangrenous appendix or a leaking ulcer. Such a patient admitted at midday or midnight requires immediate attention. This is no case in which to await the leisurely arrival of the time for routine round making even though the patient may not seem very ill.   Unfortunately, in too many instances hours elapse before hospital physicians and days before community physicians become convinced that this medical condition possesses real emergency characteristics.   For well known anatomical reasons

left popliteal embolic obstructions are more frequent than right (McKechnie and Allen 3 : 2 [1]).

Pain caused by spasm and ischemia is not always the first symptom nor is it always very severe. Perhaps in less than 60 per cent of all cases, particularly in thrombosis, is early severe pain experienced. Diagnosis may be

TABLE I

	Sex	Age	Vessel	Time Elapsed	Cardiac Lesion	Original Cause of Occlusion	Result
J. W.	M	41	Rt. Pop.	1½ hours	Mitral stenosis with fibrillation	Embolism	Disch. 45th day
J. W. (2nd admission, 2nd occlusion)	M	41	Rt. Pop.	3 hours	Mitral stenosis with fibrillation	Embolism	Death 5th day
I. B.	F	79	L. Pop.	13½ hours	Arteriosclerosis	Thrombosis	Disch. 90th day
A. W.	F	60	L. Pop. Rt. Pop. Mesenteric	30 days 2¾ hrs.	Mitral stenosis with fibrillation	Embolism	Death 6th day
A. S.	F	47	L. Pop.	10 days	Mitral stenosis with fibrillation	Embolism	Disch. 45th day
W. T.	M	74	L. Pop.	3 days	Arteriosclerotic heart	Thrombosis	Death 7th day
I. G.	M	46	L. Pop.	14 days	Myocardial degeneration	Thrombosis	Disch. 48th day
L. C.	M	56	R. Pop.	30 days	Coronary infarction	Embolism	Disch. 27th day
J. L.	M	73	R. Pop.	7 days	Coronary infarction	Embolism	Disch. 62nd day
H. S.	M	68	R. Pop.	2 weeks	Myocardial degeneration	Thrombosis	Amputation. Disch. 38th day
C. S.	M	65	L. Pop. rt. leg 1 yr. earlier	8 days	Myocardial degeneration. Auricular fibrillation	Embolism	Amputation 11th day. Death 27th day
H. C.	M	49	Rt. Pop.	6–8 hrs.	Coronary occlusion	Embolism	Death 16 hrs. Coronary obstruction

much delayed if one always waits for the appearance of pain. Numbness, paresthesia, pallor and coldness may precede pain, and these in popliteal obstruction may be wholly confined to the toes or foot. Loss of motion with distention of the superficial veins of the limb are early symptoms, the former occurring when ischemia approaches tissue asphyxia. In the absence of instruments of precision, pain, paresthesia and coldness in any portion of the lower extremity with the persistence of a femoral pulsation suggest that the obstruction is in one of three places, i.e., at the point of departure of the pro-

funda femoris from the main trunk, at the bifurcation of the popliteal, in the posterior tibial or in the smaller vessels of the plantar arch.   The posterior tibial is obstructed in approximately 10 per cent of cases of arterial occlusion. We have often observed evidences of carelessness in so simple a step as searching for the presence of a femoral pulsation on the affected side.   A mid-thigh amputation for the relief of gangrene of a foot would, of course, be futile if the obstruction be at the bifurcation of the aorta.   On the other hand, the proximal clot may be so extensive that circulation may be destroyed many centimeters above the site of the original embolism.   The oscillometer is of much use in verifying clinical information as to changes in temperature as secured by the palpating hand.   The use of the histamine or of the salt solution wheal in the absence of histamine serves to confirm the findings of · the oscillometer.   The surface temperature apparatus is also highly useful. The elevation and depression of a part by revealing the rapid emptying and filling of vessels serve to indicate the presence of obstruction without definitely locating it.   The salient features of the patients comprising this series appear in table 1.

Of the 11 cases in this series, eight were male and three female.   The average age was 59.   The right popliteal was occluded in seven instances, the left in five, both in one (six occlusions in three patients).   In one patient the right popliteal artery was embolized twice.   The cause of the obstruction was embolism in eight instances, thrombosis in four.   In one patient (C. S.) the right popliteal was embolized and the leg amputated 16 months prior to embolism of the left·popliteal.   The cardiovascular condition which existed was mitral stenosis with fibrillation in four cases, myocardial disease with fibrillation in one case, arteriosclerosis in three and coronary occlusion in three.   Three case' histories have been selected to illustrate some of the diagnostic and therapeutic points set down in this paper.

CASE REPORTS

Case 1. A. W., female, aged 60, was admitted to the hospital February 3, 1941 complaining of pain, loss of sensation, and coldness of the left leg.

Four weeks before admission, while recovering from an upper respiratory infection, she suddenly experienced a sharp pain on the inner aspect of the left leg near the knee which was quickly followed by pain in the toes and a feeling of numbness and coldness of the entire foot.

The past medical history revealed that the patient suffered with a phlebitis of the left leg following a nephrectomy at the age of 35.   She had had rheumatic fever as a child.   For several years she had experienced dyspnea on exertion.

Physical examination disclosed a woman apparently in severe pain with fever and evidences of toxemia.   The lungs were clear.   The heart was enlarged and was actively fibrillating. · The first sound was slapping, but no distinct presystolic murmur could be heard.   The left leg below the knee was cold and cyanotic.   Neither the left popliteal nor the dorsalis pedis artery could be palpated.   Pulsations in both femorals were present.   Oscillometric variations below the left knee were absent. Two days after admission the same symptoms occurred in the right leg.   A diagnosis of embolism, first of the left and then of the right popliteal artery, was made.   The

patient was heparinized, paravertebral block was done, and the Pavex boot was employed one hour twice a day to both legs since the patient's condition did not warrant radical treatment. Acute abdominal pain developed on the fifth day after admission to the hospital and a diagnosis of mesenteric embolism was made. The patient died on the sixth day of her hospital stay.

Autopsy confirmed the presence of an older embolism in the left, and a fresh occlusion of the right popliteal artery. The aorta was patulous. The superior mesenteric was closed by a fresh embolus and gangrene of a loop of bowel with peritonitis was present.

This patient with a bilateral popliteal obstruction illustrates the danger inherent in a delayed diagnosis of vascular occlusion, one of the common causes of death (mesenteric obstruction with peritonitis), and some of the methods of treatment commonly employed.

Case 2. J. W., male, aged 41, was admitted to the Jewish Hospital on December 13, 1940 complaining of a productive cough and fever. His temperature was 102.4° F., pulse 112, respirations 32. While at home after several days of an upper respiratory infection he had experienced a chill, substernal pain and had become very ill. He had had rheumatic fever as a child. Tonsillectomy was performed eight years ago. Physical examination disclosed a consolidation at the right base. Liver dullness extended a finger's breadth below the costal margin. There was a presystolic and systolic murmur present with a thrill best felt over the precordium at the level of the fourth and fifth ribs in the nipple line. After two days of the administration of sulfapyridine the temperature fell to normal and remained so for four days. On December 15 the patient began to fibrillate. On December 19, while asleep, he experienced a sudden, excruciating pain in the right leg (region of the popliteal space). All the signs and symptoms of popliteal obstruction appeared (vide supra).

Within one and a half hours treatment was begun which consisted of paravertebral block (L1–2–3), heparinization, the use of papaverine, the alternating pressure cuff, and the thermostatic cradle. One hundred ninety-five c.c. of heparin were given by vein in the next four days, the clotting time (venous) varying from 15 minutes to one hour. Blocking of the sympathetic roots was performed three times on succeeding days.

Papaverine hydrochloride (gr. ½) was administered mostly intravenously every four hours for a period of three weeks.

For 24 hours no dorsalis pedis pulse could be felt nor were there oscillometric variations below the knee or at the ankle. On December 20, an oscillometric variation of ⅓ was noted at the right ankle. In two days a distinct·pulsation could be felt in the dorsalis pedis artery, the leg became warmer and regained its color, and the subjective symptoms of numbness and tingling gradually disappeared. The patient still fibrillating was discharged from the hospital on February 3, 1941.

On November 9, 1941 this patient was readmitted to the hospital after 10 months of comparative comfort at home during which he performed light work in his grocery store. The patient now had a fever of 106° F., pain in the chest, and a return of pain in the right ankle and in the right popliteal space. The previously described symptoms and signs of right popliteal occlusion were again present. Rapid auricular fibrillation was present and the patient was now very critically ill.

A diagnosis of pulmonary infarction with pneumonia and popliteal occlusion with cardiac decompensation was made. Paravertebral block, heparinization, and the use of vasodilators and sulfadiazine were at once instituted. Despite all measures, death occurred on November 13, 1942.

Autopsy disclosed the presence of chronic rheumatic aortic and mitral endocarditis. In the left auricle there was a patch of acute ulcerative endocarditis, three centimeters in diameter, on which there still remained large and small clots which appeared to be the source of the repeated popliteal emboli. There were old and new infarctions of the lungs and spleen. The first popliteal embolus had been organized and endothelialized, the lumen of the vessel at its bifurcation being occluded by a fresh embolus.

In this patient the following interesting points are illustrated: a double obstruction of the right popliteal artery, an unusual source of thrombotic emboli in the presence of the more common one (mitral stenosis with auricular fibrillation), and recovery from an obstruction of the popliteal artery following the use of conservative measures.

Case 3. A. S., aged 47, female, awoke at 4 a.m. on February 5, 1941, complaining of pain, coldness, numbness and loss of motor power in the left leg below the knee. The leg was treated by the application of hot saline packs. There was no relief from the above symptoms. On February 15 she noticed discoloration of a bunion on the inner aspect of the first metatarsal joint. The patient was admitted to the hospital on this day.

On examination the left leg was cold below the knee. The left foot was cyanotic. There was no popliteal or dorsalis pedis pulsation. No oscillometric variations were secured below the knee. There was a presystolic mitral murmur and auricular fibrillation. A diagnosis of embolism of the left popliteal artery was made.

The patient was given papaverine hydrochloride (gr. ½) every fourth hour by mouth for 21 days. The alternating pressure and release cuff was used continuously for 10 days. The remainder of the treatment was symptomatic. The patient was discharged on April 1, 1941, with but a small patch of dry gangrene on the outer aspect of the first toe on the affected foot.

Treatment. The treatment to be employed may be of two types, the conservative and the radical. Some clinicians prefer the immediate surgical approach and when the popliteal or brachial vessels are affected this operation seems not too difficult. There are not a few instances in which the immediate removal of an embolus from the aortic, the popliteal or the brachial has proved most effective. Because the source of arterial embolism is so often the heart and because of the great tendency to recurrence, we are strongly of the opinion that the conservative handling of these cases in comparison with one more radical often offers an equal if not a greater chance of saving the limb of the patient. The aims of the conservative treatment are two: the relief of vascular spasm and the establishment of collateral circulation. To relieve vascular spasm, paravertebral block, papaverine and various physiotherapeutic measures which particularly aim to maintain the temperature of the part are employed. To prevent thrombosis and assist in the establishment of collateral circulation, heparin, the passive vascular exercise machine (Pavex), and the Collins-Wilinsky apparatus are employed.

The first concern of the physician when an embolus lodges is the relief of vascular spasm by blocking the sympathetic roots. This, in the case of popliteal obstruction, should be attempted by injecting the first, second and third lumbar roots. Although in the hospital this procedure is usually

performed by a surgeon familiar with the regional anatomy involved, a physician with but little practice may perform this injection satisfactorily. Paravertebral block should probably be performed daily for four or five days following the lodging of an embolus. It is gratifying after a successful block to note the improvement in color and temperature, and the lessening of pain which result when a spastic vessel segment is thus relaxed. Papaverine hydrochloride should be administered intravenously in one-half to three-quarter grain doses every four hours night and day. Denk,[7] in 1934, reported the recovery of seven out of 10 patients with the use of papaverine alone, and Herman and Reid[8] a perfect record of 10 out of 10 patients by using Pavex alone. Such results are most unusual. The limb is immediately placed beneath a thermostatically controlled cradle with the temperature set at about 98° F. The common metal or wooden cradle with electric bulb suspended from its roof is incapable of providing an evenly regulated temperature. To expose the limb to a high degree of temperature is to accelerate metabolism in an already impoverished tissue. The limb should be encased in a flannel operating room boot and of course pressure points prevented.

The prevention of the formation of proximal clots and perhaps the promotion of the seepage of blood through a partially obstructed channel by heparinization should be attempted early. It has been the custom of the writer to administer at once 5 c.c. (5,000 units) of heparin intravenously in 100 c.c. of salt solution, allowing three to five minutes for its entrance into the vein. The apparatus consists of a ureteral catheter placed within the vein of the non-affected foot. This is connected to the tubing from the container by the insertion in the end of the catheter of an 18 gauge needle. The advantage of an arc of 15 to 20 inches for movement of the limb is obvious, and local irritation and the likelihood of infection at the point of injection are reduced to a minimum. Ten c.c. of heparin are added to 500 c.c. of salt solution and allowed to enter the vein at the rate of 2 to 4 c.c. a minute. Coagulation time, taken twice a day, is maintained at about 20 minutes. Passive vascular exercise is given one-half hour twice a day with the gauge set at plus 40 for pressure and minus 30 for vacuum. The Collins-Wilinsky alternating pressure cuff is applied to the thigh continuously except when passive vascular exercise is being administered. If embolectomy is performed, heparinization is always necessary. The writer is of the opinion that the recent suggestions of some clinicians that coagulation time may be maintained at a satisfactory level by sixth hour injections of 5 c.c. of heparin are not practicable. In his hands the periodic intravenous injection of heparin produced an irregular coagulation time curve.

SUMMARY

1. Eleven cases of popliteal occlusion were presented.
2. Comments on the symptoms as related to diagnosis were made.

3. The necessity of early diagnosis was stressed, it being stated that treatment, whether it be radical or conservative, must be begun within the first six hours if good results are to be expected.

4. The value of a carefully planned conservative routine was pointed out.

5. The technic of heparinization was briefly described.

BIBLIOGRAPHY

1. McKechnie, R. E., and Allen, E. V.: Sudden occlusion of arteries of the extremities, 100 cases of embolism or thrombosis, Surg., Gynec. and Obst., 1936, lxiii, 231–234.
2. Seifert, E.: Die Deutung des Schmerzes bei der arteriellen Embolie, Deutsch. Ztschr. f. Chir., 1931, ccxxxii, 187–198.
3. Lewis, Sir Thomas: Vascular disorders of the limbs, 1936, Macmillan Co., New York, N. Y., p. 29.
4. Gossett, A., Bertrand, Ivan, and Patel, Jean: Sur la physio-pathologie des embolies arterielles des membres, Ann. d'anat. path., méd.-chir., 1932, ix, 841–862.
5. Hindmarsh, J., and Sandberg, I.: Forty-five embolectomies (Retrospective survey with special regard to after effects), Acta chir. Scandin., 1936, lxxviii, 81–91.
6. DeTakats, D.: Vascular accidents of the extremities, Jr. Am. Med. Assoc., 1938, cx, 1075–1081.
7. Denk, W.: Zur Behandlung der arteriellen Embolie, München. med. Wchnschr., 1934, lxxxi, 437–439.
8. Herman, L. G., and Reid, M. R.: Passive vascular exercise treatment of peripheral obliterative arterial disease by rhythmic alterations of environmental pressure, Arch. Surg., 1934, xxix, 697–704.

CHANGES OF THE WATER TOLERANCE TEST IN HEPATIC DISEASE *

By David Adlersberg, M.D., and Charles L. Fox, Jr., M.D.,
New York, N. Y.

It has long been recognized that liver diseases are frequently associated with disturbances in water metabolism. Hanot made the well known statement "Il y a un oedème hépatique comme il y a un oedème renal." Gilbert and Lereboullet [1] observed in some cases of liver disease oliguria, "opsiurie hépatique," which in severe cases may lead to anuria. Later, experimental observations, particularly by E. P. Pick and his coworkers,[2] established the important rôle of the liver in water metabolism. Analogous clinical observations have also been made.[3] It seemed that the disturbance of water metabolism would be of diagnostic significance if it could be correlated with the nature and extent of hepatic damage.

Experimental Hepatic Damage

Hepatic damage was produced in dogs by one of us (D. A.) by repeated administration of phosphorus and histamine.[3] In the early stages of in-
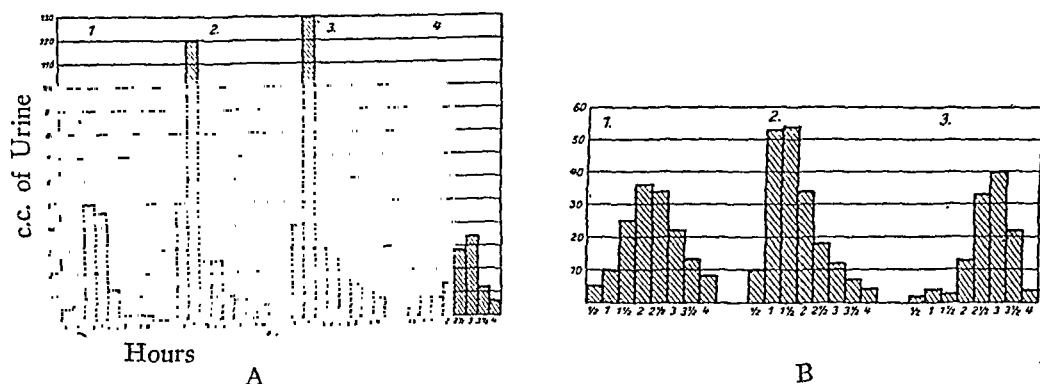
Fig. 1. Progressive changes of the water metabolism in dogs caused by hepatic damage in chronic phosphorus and histamine intoxication.
A. Water tolerance test in experimental phosphorus intoxication.

1. Control after 200 c.c. tap water given by stomach tube to fasting dog (weight 10 kg.)
2. and 3. Examples of early hepatic damage (second week). Exceeding and accelerated diuresis, "shift to the left."
4. Example of later stages (fifth to sixth week). Diminished and delayed diuresis, "shift to the right."

B. Water tolerance test in experimental (chronic) histamine intoxication.

1. Control after 200 c.c. tap water given by stomach tube to fasting dog (weight 6.2 kg.)
2. Example of early stage (first week). Accelerated diuresis, "shift to the left."
3. Example of later stages (third week). Delayed diuresis, "shift to the right."

toxication, with mild hepatic damage, water intake caused an early and excessive diuresis (figure 1), the curve of which is characterized by a "shift to the left." In later stages with considerable hepatic damage, diuresis was delayed and diminished and showed a "shift to the right" in the diagram. Furthermore, water retention in the tissues was demonstrated by the intradermal wheal test and by chemical determinations.[3]

CLINICAL OBSERVATIONS

This information was then applied to a clinical study of liver disease. To make the results comparable a uniform technic of performing a water
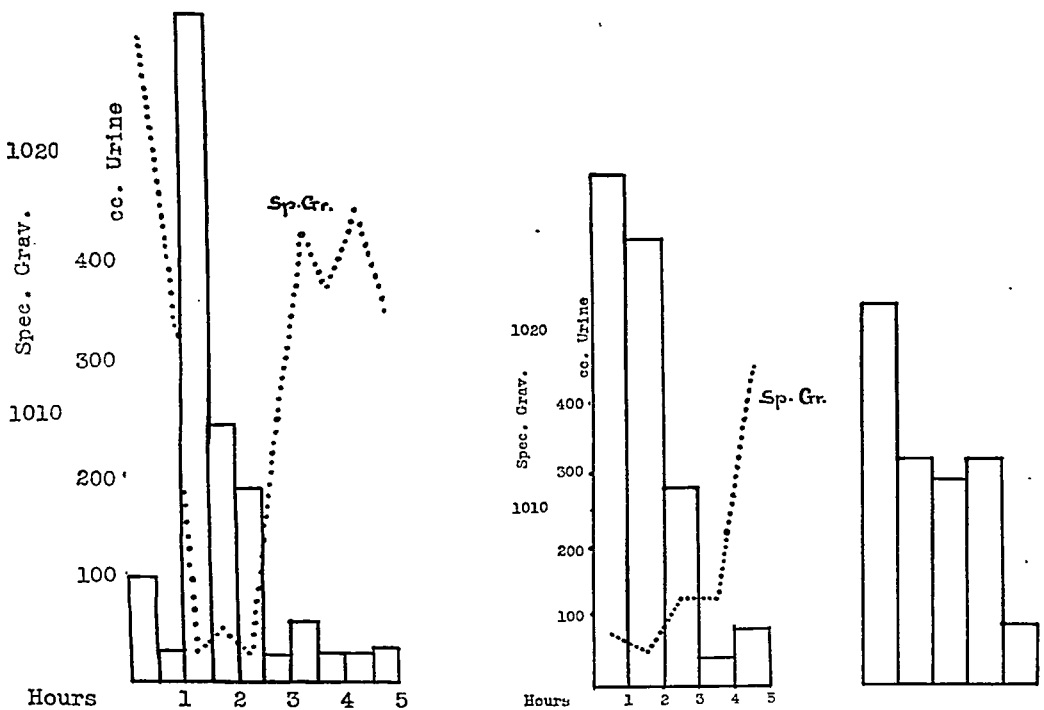
FIG. 2. (*Left*) Normal water tolerance test in man. In this example the total elimination is 1355 c.c. in five hours; rate of diuresis is characterized by maximum output during the second and third hour; spec. gravity (dotted line) varies inversely with water output, the minimum is 1.001.

FIG. 3. (*Right*) Early stage of arsphenamine hepatitis.

A. First water tolerance test (12.4). Total elimination 1780 c.c. Icteric index 60, serum cholesterol 189 mg. per cent.
B. Second water tolerance test, one week later (12.11). Total elimination 1455 c.c. Icteric index rose to 125.

Note early exceeding diuresis in A with marked shift to the left. A week later the shift to the left persists. The findings resemble early experimental hepatitis.

tolerance test was adopted. Fasting subjects were given 1500 c.c. of tap water within 20 to 30 minutes. The bladder was emptied by voiding, and urine specimens were obtained every 30 minutes for five hours. The volume and specific gravity of each specimen were measured and these data were

arranged in a diagram as shown in figure 2, which is representative of the tests performed on 30 healthy control subjects. On this basis, the following criteria of a normal water tolerance test can be formulated. They correspond to similar tests for renal function.[4]

A. Total elimination in five hours: 1200–1500 c.c.
B. Rate of diuresis: The output uniformly rises to a maximum during the second and third hours and then declines.
C. Specific gravity: Fluctuates inversely with the urinary output; the minimum (1.000 to 1.003) coincides with the maximum output during the second and third hours.

The patients with liver disease who were studied, mostly with icterus, may be divided into two general groups: one with parenchymatous liver disease and one without. The diagnosis was established by the usual methods and tests: history and physical examination, roentgenographic examination, icteric index, galactose and sodium benzoate tolerance tests, cholesterol-cholesterol ester ratio, and the d-lactate clearance test. In some cases the diagnosis was verified by aspiration biopsy.

As a result of these many sided investigations it was possible to select a group of patients in whom all the evidence indicated the presence of parenchymatous liver disease (acute and subacute hepatitis). Furthermore, there were included for this study only patients who showed no renal or cardiovascular changes that might influence their water metabolism. In all cases the values of urea nitrogen (or non-protein nitrogen) and of proteins in the blood were normal; the urine was free of albumin and showed the ordinary range of variation in specific gravity. No cases of ascites were included. None of the patients presented signs of the so-called hepatorenal syndrome. In this selected group of patients water tolerance tests were done at intervals. The various stages of their disease were compared with alterations in the water tolerance test in terms of total elimination, rate of diuresis, and fluctuation of specific gravity.

A. Total elimination in five hours. In mild degrees of hepatitis elimination was normal (1200–1500 c.c.) or increased (1800 c.c.). In severe hepatitis the output was diminished (300 c.c. to 1000 c.c.). The retention of water in this test roughly paralleled the severity of the disease.

B. Rate of diuresis. In cases of mild hepatitis the rate of diuresis increased uniformly to the maximum at the second or third hour (as in normals). Not infrequently the rate was accelerated so the maximum occurred in the first hour. When plotted, the peak of diuresis was then shifted to the left. In severe hepatitis this shift to the left frequently appeared at the onset and in later stages was replaced by delayed diuresis, without the usual fluctuations in volume and specific gravity of the specimens. The graphic presentation of the data failed to show the peak at the mid period; in some cases the curve of diuresis was shifted to the right.

C. Specific gravity. In cases of mild hepatitis associated with normal

or increased water elimination, the minimum reached 1.000 to 1.003. In cases of diminished diuresis, the minimum specific gravity, 1.004 to 1.008, was shifted to the left or right and coincided with maximum diuresis.

Parenchymatous Liver Disease. This group comprised 23 patients on the wards of the hospital. A few typical examples are presented below.

<div align="center">CASE REPORTS</div>

C. G., white female, aged 34, was admitted to the hospital following a street accident and transferred to medical wards because of jaundice. The patient was receiving antisyphilitic treatment in the dispensary. The last injection of neo-arsphenamine had been given two weeks previously and was followed by a red, itching eruption. The skin and sclerae were slightly icteric, liver and spleen were not palpable. The blood count was normal, the icteric index 60, cholesterol 189 mg. per cent, non-protein nitrogen 25 mg. per cent. Takata-Ara test one week later was moderately positive. Urine contained bilirubin and was otherwise normal. The diagnosis was early arsphenamine hepatitis.

The water tolerance tests performed on admission and one week later are shown diagrammatically in figure 3. The diuresis exceeded the intake in the first test and declined to normal in the second. In both instances the peak of the diuresis occurred in the first hour, resulting in a marked shift to the left of the curve. The specific gravity was similarly shifted to the left. The changes in the water tolerance test in this case of very early acute hepatitis bear a striking resemblance to those in early experimental hepatitis (figure 1).

M. V., white female, aged 57, was admitted with a history of anorexia, malaise and jaundice of two months' duration. The skin and sclerae were icteric. The liver was palpated 2 cm. below the costal margin and later diminished in size and became impalpable. The blood count was normal, the icteric index 23 to 40, cholesterol 312–440 mg. per cent, cholesterol esters 110–150 mg. per cent, Takata-Ara 4 plus, sodium benzoate test positive (less than 0.5 gm.). The urine showed a very faint trace of albumin, bilirubin, and urobilinogen up to 1 : 160. The diagnosis was toxic hepatitis, possible subacute yellow atrophy.

The water tolerance test (figure 4) showed marked diminution of water elimination; the total output was 384 c.c. The rate of diuresis was characterized by a lack of the normally observed variations resulting in a relatively flat curve. The specific gravity showed markedly impaired dilution.

L. H., white female, aged 48, was admitted because of weakness, moderate weight loss and jaundice of two months' duration. The skin and sclerae were icteric. The liver was markedly enlarged, extending to the umbilicus, and felt firm and nodular. The spleen was also palpable 4 cm. below the costal margin. The blood count was normal, the icteric index ranged from 15 to 40, serum proteins 7.1 per cent, cholesterol 170–460 mg. per cent, cholesterol esters trace to 110 mg. per cent, galactose test was positive (4.2 to 9.0 gm.) on many occasions, sodium benzoate and d-lactate tests were also positive. The urine contained no albumin, urobilinogen up to 1 : 320 and bilirubin. Aspiration biopsy showed "chronic and acute interstitial hepatitis, liver cell degeneration, striking periportal infiltration with leukocytes." The diagnosis was cholangitic cirrhosis with superimposed hepatitis.

The water tolerance test was followed in this case over a period of four months (figure 5) along with the usual clinical tests. During this time there were fluctuations in the intensity of the disease. The earliest water tolerance test showed a shift to the left. Two weeks later when the jaundice had increased, this shift persisted and the total elimination was diminished. When the icterus decreased five

days later and the galactose test showed improvement, the water tolerance test returned to normal with a normal diuresis pattern. This improvement in the patient's condition was only temporary. Progressive impairment of liver. function recurred and was associated with diminished water output and lack of the usual variations in diuresis and specific gravity (hepatitis pattern). Then, two months later, with improvement of liver function, there was also an almost normal water tolerance test pattern.

Similar changes of the water elimination and the diuresis pattern were observed in the next case of arsphenamine hepatitis.
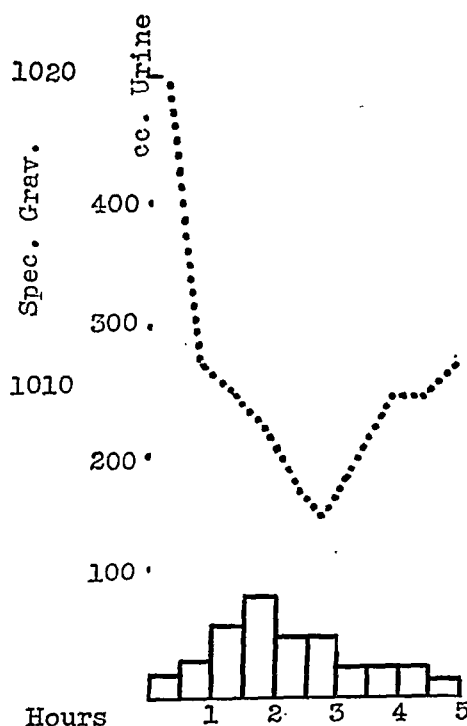
Fig. 4. Typical case of severe hepatitis. Water tolerance test shows total elimination of only 384 c.c., less than half normal; rate of diuresis is abnormal, marked variations of the individual specimens are absent; dilution is impaired, lowest specific gravity is 1.006. Icteric index was 23. Galactose tolerance test and sodium benzoate test were 4 plus positive.

E. V., a Puerto Rican male, aged 30, was admitted with itching and jaundice of two months' duration. The antisyphilitic treatment began 15 months previously and was stopped six months prior to admission because of a generalized eruption. There was intense icterus, the liver was palpable 2 cm. below the costal margin, and the spleen was palpable 8 cm. below the costal margin. The blood count was normal, the serological tests for syphilis were negative, the icteric index was 27, and the cholesterol 165–190 mg. per cent with cholesterol esters 32–80 mg. per cent. The galactose. test was positive (6.1–7.1 gm.), sodium benzoate 0.8–2.5 gm. The urine was positive for arsenic, bilirubin, and urobilinogen up to 1 : 160. The diagnosis was arsenical hepatitis of long duration.

Slow, progressive impairment is indicated in the first three curves by the reduced output and diminished fluctuations of volume and specific gravity (figure 6). There was no shift to the left. Coincidental with clinical improvement there was also improvement of the water tolerance test.

Obstructive Icterus. The second group consisted of 10 cases of obstructive jaundice caused by stone or neoplasm, one case of congenital hemolytic icterus and one case of "Banti's syndrome." In these cases the water tolerance tests were within normal limits. The diuresis pattern in none of the cases resembled that found in hepatitis. As examples, the curves are presented of one case of obstructive jaundice caused by carcinoma of the
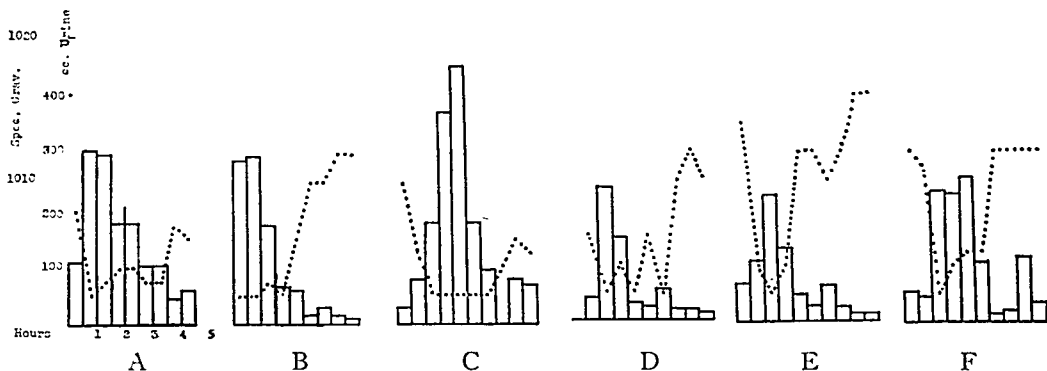
FIG. 5. Changes of the water tolerance test in the course of a long-standing chronic hepatitis.

A. First water tolerance test (10.29). Total elimination 1410 c.c. Icteric index 21, serum cholesterol, 460 mg. per cent, esterified cholesterol 110 mg. per cent. Galactose tolerance test: 8.1 gm. D-Lactate test: 2 plus positive.
B. Second water tolerance test (11.11). Total elimination 947 c.c. Icteric index 40, serum cholesterol 275 mg. per cent, esterified cholesterol 60 mg. per cent. Galactose tolerance test: 5.5 gm.
C. Third water tolerance test (11.18). Total elimination 1544 c.c. Icteric index 18. Galactose tolerance test: 4.2 gm. General condition markedly improved.
D. Fourth water tolerance test (12.6). Total elimination 591 c.c. Clinically, exacerbation of symptoms for past 7–8 days.
E. Fifth water tolerance test (1.28). Total elimination 732 c.c. Icteric index 15, serum cholesterol 170 mg. per cent, esterified cholesterol only in trace. Galactose tolerance test: 9.0 gm. D-Lactate test: 4 plus positive. Patient is gravely ill.
F. Sixth water tolerance test (2.22). Total elimination 1101 c.c. Icteric index 10, serum cholesterol 225 mg. per cent, esterified cholesterol 47 mg. per cent. D-Lactate test: 2 plus positive. Patient is slowly improving.

Note impaired dilution and shift to the left in B with improvement in C, progressive impairment of water tolerance test in D and E coinciding with the clinical picture and then gradual improvement in F.

head of the pancreas, the case of congenital hemolytic icterus, and the case of "Banti's syndrome" (figure 7).

Not infrequently, obstructive jaundice may be associated with hepatic parenchymal damage. These cases present the usual clinical evidence of obstructive icterus whereas laboratory data suggest parenchymal damage. The water tolerance test likewise may show a pattern of hepatitis in these cases. An example of this is shown in figure 8. Initially there was reduced output, delayed diuresis and no marked decrease in specific gravity. The pattern showed marked shift to the right. Later with increasing jaundice, impairment manifested itself by early diuresis with shift to the left. In the last curve, the output was normal but the shift to the left persisted.
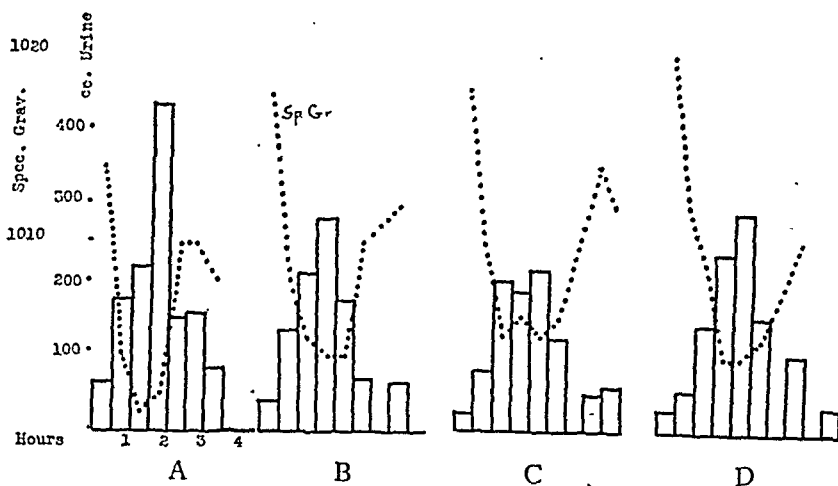
Fig. 6. Progressive impairment followed by gradual improvement in a moderate arsphenamine hepatitis.

A. First water tolerance test (1.23). Total elimination 1292 c.c. Icteric index 27, serum cholesterol 165 mg. per cent, esterified cholesterol 42 mg. per cent. Galactose tolerance test: 7.1 gm. Sodium benzoate test: 0.8 gm.

B. Second water tolerance test (1.28). Total elimination 979 c.c. Icteric index 25, serum cholesterol 175 mg. per cent, esterified cholesterol 30 mg. per cent. Galactose tolerance test: 8.2 gm.

C. Third water tolerance test (2.17). Total elimination 937 c.c. Icteric index 27, serum cholesterol 190 mg. per cent, esterified cholesterol 32 mg. per cent. Galactose tolerance test: 9.1 gm.

D. Fourth water tolerance test (2.25). Total elimination 1051 c.c. Icteric index 20. Sodium benzoate test: 2.5 gm. General condition gradually improving.

Note reduction of total output and impaired dilution, most marked in C, followed by slight improvement in D coinciding with the clinical picture.

DISCUSSION

The observations described above together with the results of the animal experiments [3] confirmed the old clinical impression that parenchymatous hepatic damage is associated with profound changes in water metabolism. This suggests the possibility of using the impairment of water metabolism as a diagnostic sign of disturbed liver function. It is generally acknowledged that impairment of some of the many functions of the liver may occur without changes in the others. This has been shown for experimental hepatic damage caused by phosphorus and carbon tetrachloride [5] as well as in human disease.[6] Accordingly, it was of interest to compare the results of the usual liver function tests with the water tolerance test. Since all of these cases had a galactose test, the following comparison of the 23 cases of hepatitis may be of interest.

Galactose and water tolerance test positive .... 17 cases
Galactose and water tolerance test negative .... 2 cases
Galactose test positive and water tolerance test negative .... 4 cases

Total .... 23 cases

It is evident that in this small group of cases the simple water tolerance test compares rather favorably with the more elaborate galactose test.

It must be realized that an impaired water tolerance test may be taken as
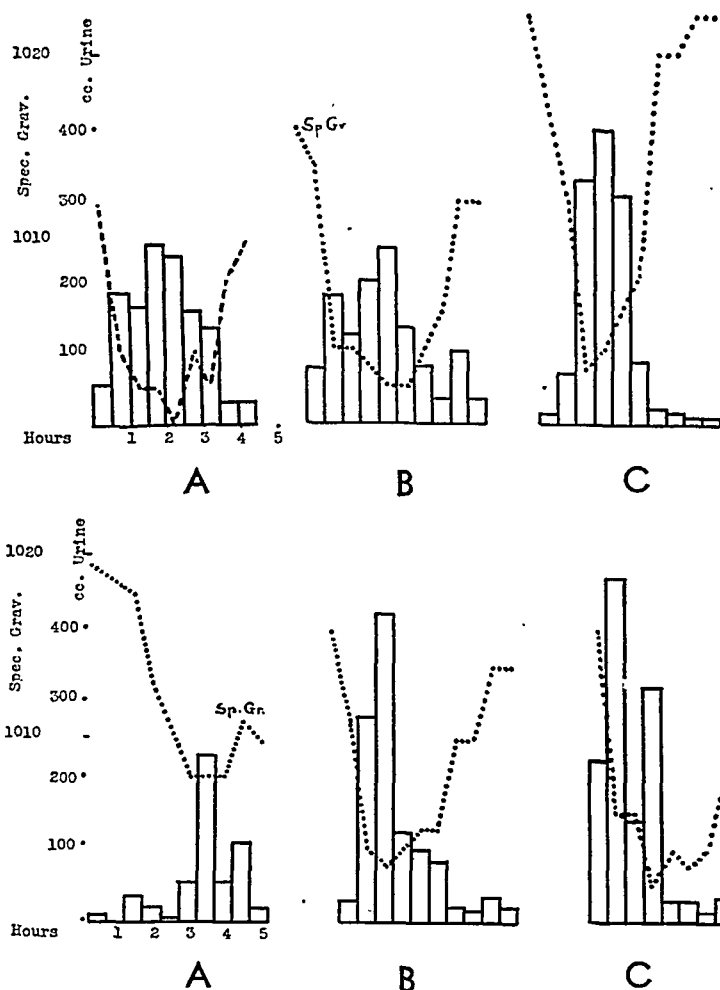
FIG. 7. (*Above*) Other types of icterus and hepatic disease without changes in water tolerance test.

A. Obstructive jaundice, carcinoma of head of the pancreas. Water tolerance test showed total elimination of 1209 c.c. Icteric index 30, serum cholesterol 340 mg. per cent, esterified cholesterol 83 mg. per cent. Galactose tolerance test: 0.8 gm.
B. Congenital hemolytic icterus. Water tolerance test showed total elimination of 1185 c.c. Icteric index 23, serum cholesterol 215 mg. per cent, esterified cholesterol 90 mg. per cent. Galactose tolerance test: 0.5 gm.
C. Hepatosplenomegaly, Banti's syndrome. Water tolerance test showed total elimination of 1268 c.c. Icteric index 6, serum cholesterol 225 mg. per cent,. esterified cholesterol 78 mg. per cent. Galactose tolerance test: 3.0 gm. Sodium benzoate test: 2.4 gm.

Note in all three cases: Elimination of water, rate of diuresis and dilution are normal.

FIG. 8. (*Below*) Alteration of the water tolerance test in hepatitis superimposed on common duct neoplasm.

A. First water tolerance test (3.13). Total elimination 538 c.c. Icteric index 23, serum cholesterol 290 mg. per cent, esterified cholesterol 87 mg. per cent. Galactose tolerance test: 5.0 gm. D-Lactate test: 2 plus positive.
B. Second water tolerance test (3.18). Total elimination 1131 c.c. Icteric index 28.
C. Third water tolerance test (3.24). Total elimination 1361 c.c. Icteric index 30, serum cholesterol 320 mg. per cent, esterified cholesterol 145 mg. per cent. Galactose tolerance test: 3.6 gm.

Note in A in addition to reduced output and impaired dilution, the delayed rate of diuresis resulting in a shift to the right; in B water elimination is still impaired although output is increased and dilution better, the rate of diuresis is accelerated causing a shift to the left; in C the output is normal but the shift to the left persists.

an indication of liver damage only when other factors that can affect water elimination are absent. These factors are: hyperpyrexia, cachexia, dehydration, edema, hypoproteinemia, cardiovascular and renal disease, certain endocrinological diseases and hepatorenal syndrome. The presence of ascites obviously precludes the use of the water tolerance test to estimate the hepatic damage in cases of liver cirrhosis. In other words, when any of these conditions are present, the water tolerance test cannot be used as a measure of hepatic damage. This distinct disadvantage is only partially counterbalanced by the simplicity of the test. It can be performed at no cost, without special apparatus at the doctor's office or in the patient's home as well as in a hospital.

The alteration of the water tolerance test in cases of hepatic damage is only one sign of a more profound alteration of water metabolism. Another sign is the not infrequent, latent or manifest edema which may progress to anasarca and ascites at the height of the disease.

SUMMARY

The use of a water tolerance test in liver disease is described. In the absence of other factors influencing water metabolism, a positive water tolerance test is suggestive of hepatic damage.

BIBLIOGRAPHY

1. GILBERT, A., and LEREBOULLET, P.: Des urines retardées (opsiurie) dans les cirrhoses, Compt.-rend. Soc. de biol., 1901, iii, 229–279.
2. PICK, E. P.: Harvey Lectures, New York, 1929–1930.
   MOLITOR, H., and PICK, E. P.: Die Bedeutung der Leber für die Diurese, Arch. f. exper. Path. u. Pharm., 1923, xcvii, 317–343.
   MOLITOR, H., and PICK, E. P.: Ueber zentrale Regulation des Wasserwechsels. I. Mitteilung. Der Einfluss des Grosshirns auf die Pituitrinhemmung, Arch. f. exper. Path. u.-Pharm., 1925, cvii, 185–191.
   MOLITOR, H., and PICK, E. P.: Ueber zentrale Regulation des Wasserwechsels. III. Mitteilung. Ueber den zentralen Angriffspunkt der Diuresehemmung durch Hypophysenextrakt, Arch. f. exper. Path. u. Pharm., 1926, cxii, 113–121.
3. ADLERSBERG, D.: Zur Rolle der Leber im Wasserhaushalt, Wien. Arch. f. inn. Med., 1934, xxv, 269–282 and 401–462.
   ADLERSBERG, D., and PAUL B.: Ueber Veraenderungen des Wasserhaushaltes im Anaphylaktischen und im Histaminschock, Ztschr. f. exper. Med., 1933, xcii, 293–303 and 304–310.
4. LEBERMANN, F.: Ueber Nierenfunktionspruefungen, Ergebn. d. inn. Med., 1929, xxxv, 465–518.
   LEBERMANN, F.: Der Wasserversuch und seine klinische Bedeutung, Ergebn. d. inn. Med., 1930, xxxviii, 289–436.
   LEBERMANN, F.: Ueber Nierenfunktionspruefungen, Ergebn. d. inn. Med., 1932, xlii, 1–99.
5. ADLERSBERG, D., and MINIBECK, H.: Zur Auswertung der Leberfunktionsproben im Tierversuch (Galaktoseprobe, Wasserversuch, Hippursaeuresynthese bei der Phosphor- und Tetrachlorkohlenstoffvergiftung), Ztschr. f. exper. Med., 1936, xcviii, 185–200.
6. MANN, F. C.: Liver and medical progress, Jr. Am. Med. Assoc., 1941, cxvii, 1577–1582.
7. McCLURE, W. B., and ALDRICH, C. A.: Die intradermale Salzloesungsprobe, Klin. Wchnschr., 1927, vi, 1198–1201.

ON THE IMPORTANCE OF MALARIA AS A CAUSE OF FALSE POSITIVE SEROLOGIC REACTIONS *

By T. R. DAWBER, M.D., P. A. SURGEON, U.S.P.H.S.,
Stapleton, S. I., N. Y.

THE evaluation of positive serologic tests for syphilis is a problem which every physician must face. A diagnosis of syphilis is a serious matter, and its implications may be far reaching. Failure to start treatment in a known syphilitic as early as possible may well be grounds for malpractice. Equally serious and sometimes disastrous is a diagnosis of syphilis in some one who does not have the disease. From a public health point of view this may not be of much concern since in the general population of healthy individuals diagnostic errors due to false positive serologic reactions occur in only about 1 in 4000 individuals.[4]

Looked at from the individual patient's standpoint, however, such statistics mean little. No patient wants to be labeled a syphilitic unless he has the disease since he knows, or soon learns, that this entails prolonged, and unfortunately, in some hands, painful treatment with drugs which are not entirely devoid of danger. Therefore, due caution must be exercised in making every diagnosis of syphilis. In the presence of clinical or historical evidence of the disease the interpretation of positive serologic reactions will in most cases not be difficult. However, when the occasional positive reaction is reported on a patient with no history or physical findings of infection difficulties arise.

In a recent review of this subject Moore et al.[1] have very carefully indicated a method of approach to the problem. They have shown the course of study to which all suspected cases of false positive serologic tests should be subjected.

From numerous studies [1, 2, 3] it has been shown that yaws, leprosy, infectious mononucleosis and malaria are diseases in which positive serologic tests for syphilis can be frequently expected. In occasional instances other conditions, e.g., pneumonia, vaccinia, measles, and other acute febrile diseases may give rise to false positive tests.

Since yaws and leprosy are extremely infrequent diseases in the United States, it will be seen that infectious mononucleosis and malaria will be the chief causes of biologic false positive serologic reactions. Unfortunately both of these diseases are quite common and often are present in a subclinical state.

This is particularly true of chronic or latent malaria. There can be little doubt that when routine blood samples are taken from all personnel of a factory, camp, etc., certain of those taken may be infected with latent malaria.

This point has been frequently suggested but is difficult to prove. Reports on the occurrence of false positive serologic tests in malaria are all concerned with the occurrence of the positive test in known cases of the disease.[5, 6, 7] That chronic malaria without positive smear will give a positive serologic reaction is still doubted. Mohr, Moore and Eagle state [8] that a positive test may be expected "only during or shortly after the acute febrile illness."

In this paper I shall attempt to show that latent malaria may produce positive tests which may easily be mistaken for latent syphilis and that the distinction between the two conditions will not always be easy. In a review of all the cases of naturally occurring malaria seen at the U. S. Marine Hospital, Norfolk, Virginia, between July, 1936 and July, 1940 the following facts were established:

The total number of cases of malaria was 64.
The total number of cases with positive serologic tests was 19.
The number of cases definitely diagnosed as syphilis was seven.
The number of cases probably due to syphilis was four.

The number of cases with false positive serologic reactions was eight. Of these eight cases in which positive tests were found due to malaria, my attention was immediately called to the following:

CASE REPORTS

Case 1. R. C., a 20 year old white male CCC boy, was admitted to the Venereal Disease Service of the U. S. Marine Hospital, Norfolk, Virginia, on June 25, 1937.

He had been well up to five months before admission when he developed a "sore" on his penis. This had lasted for about two weeks and then subsided and disappeared. Six weeks before admission he had a sore throat and was treated for the "flu." Five days before admission he had "fever" and abdominal pain. One week before admission he had a sample of blood sent to the State Laboratory for routine test along with the remainder of the CCC camp. This blood test was reported positive. A repeat test was sent to the State Laboratory and this was also positive. At the time of admission the patient had no complaints. It was believed on admission that the patient had early latent syphilis.

Physical examination showed some injection of the pharynx and a few small palpable cervical glands. The patient remained well for the next three days. A blood test taken on the Ward on admission showed Kahn reaction was three plus, Wassermann strongly positive. On June 28, 1937 he had a chill and developed a temperature of 40.2° C. A blood smear was taken and showed tertian malaria. This was the first chill the patient had had during his entire present illness. Treatment with quinine was begun.

On 7/1/37 Kahn—3 plus   Wassermann—strongly positive
   7/8/37 Kahn—negative   Wassermann—negative
   7/12/37 Kahn—negative   Wassermann—negative
   7/19/37 Kahn—negative   Wassermann—negative

Prior to the development of the chill this patient was considered definitely syphilitic and would have been treated as such had he not fortunately developed clinical malaria.

A smear had not been taken in this case prior to the chill so that it cannot be stated definitely that he had no evidence of malaria prior to onset of chill. It is my belief that he had chronic malaria, the only manifestations of which were the positive serologic tests.

In the presence of history of penile sore with later developments of a sore throat, with the positive serologic reactions, the diagnosis of syphilis could hardly be criticized.

Case 2. J. W., a 17 year old colored CCC enrollee, was admitted to the hospital July 15, 1939. He had been well up to three days before admission when he developed a headache. He had a moderate epistaxis. Later in the day he had a chilly sensation and several more nose bleeds. During the next two days he had frequent nose bleeds and on the day before admission had another chill. At the time of admission he had no complaints.

There was no history of venereal disease. Physical examination was essentially negative. The temperature was normal on the day of admission with a maximum of 37.3° C. on the following day. The temperature then stayed normal until July 28, 1939. A blood smear was negative for malaria July 19, 1939. On July 17, 1939 Kahn reaction was 2 plus, Wassermann positive. On July 20, 1939 Kahn reaction was three plus, Wassermann positive. A specimen of blood sent to the Venereal Disease Research Laboratory at Stapleton, N. Y. showed Kline exclusion, four plus; Kline diagnostic, three plus; Kahn, negative; Wassermann, positive.

As no evidence of malaria or other acute illness appeared he was transferred to the venereal disease service with a diagnosis of probable early latent syphilis. On July 28, 1939 he had a chill and tertian malarial parasites were found on the smear. Quinine therapy was begun. On July 31, 1939 the following serologic reactions were reported: Kahn, negative; Wassermann, 1 plus, doubtful; Kline exclusion, three plus; Kline diagnostic, one plus. Repeated serologic tests on August 7, August 10, and August 14, 1939, were all negative.

In this case the patient was admitted for malaria, but during two weeks' observation no evidence of malaria or other acute febrile disease was found. Malaria was believed to be ruled out and because of positive serologic reactions he was considered syphilitic. Again, fortunately for the patient, a chill and demonstration of the parasites prevented a long course of antisyphilitic treatment for non-existent syphilis. In these two cases subclinical malaria (a better term than "chronic malaria") gave rise to positive serologic reactions which were assumed to be due to latent syphilis.

It will be seen that errors can be made in the opposite direction, since if it is assumed that all positive serologic reactions obtained during the clinical course of malaria are due to malaria, some cases of latent syphilis will be missed. It is necessary, therefore, that all positive serologic tests found during malarial infection be rechecked until the test is shown to have been falsely positive because of malaria, or else due to syphilis. In this regard the question of how long one can expect the false positive reactions to persist after treatment for malaria has been started will be raised. Kitchen and Kupper [5] found that the seropositive stage varied from eight to 66 days in inoculation malaria, but their patients were of course allowed to have repeated paroxysms and most of the cases were not treated with antimalarial drugs. Nagell and Langhans [8] state that the complement fixation test was

positive in nine out of 10 patients with inoculation malaria. They state that the test again became negative seven to 15 days after the last chill with quinine treatment.

With all the cases seen in this series the serologic reactions became negative within a period of 10 days except for one case.

Case 3. J. C., a 61 year old white male, was admitted to the hospital on November 6, 1939 with a history of chills two days before admission. On the following day he had another chill and blood smear was positive for tertian malaria. Quinine therapy was begun. No further chills occurred. The following is a list of serologic reactions found in this case:

11/8/39	Kahn—4 plus	Eagle—negative
11/9/39	Kahn—4 plus	Eagle—negative
11/11/39	Kahn—4 plus	Eagle—negative
11/13/39	Kahn—4 plus	Eagle—negative
11/16/39	Kahn—3 plus	Eagle—negative

On November 16, 1939 a blood sample was sent to Venereal Disease Research Laboratory at Stapleton, N. Y.

Wassermann—Anticomplementary, Kahn—positive.
Kline Exclusion—4 plus, Kline Diagnostic—4 plus.

11/18/39	Kahn—4 plus	Eagle—negative

On November 18, 1939 a blood sample was sent to Venereal Disease Research Laboratory at Stapleton, N. Y.

Wassermann—Q.N.S., Kahn—doubtful.
Kline Exclusion—4 plus, Kline Diagnostic—doubtful, plus-minus

11/20/39	Kahn—4 plus	Eagle—negative

On November 20, 1939 a blood sample was sent to Venereal Disease Research Laboratory at Stapleton, N. Y.

Wassermann—Anticomplementary; all others, Q.N.S.

11/25/39	Kahn—4 plus	Eagle—negative
11/27/39	Kahn—4 plus	Eagle—negative
12/13/39	Kahn—negative	Eagle—negative
1/12/40	Kahn—negative	Eagle—negative

On January 12, 1940 a blood sample was sent to Venereal Disease Research Laboratory at Stapleton, N. Y.

Kline Exclusion—negative, Kline Diagnostic—negative.
Wassermann—negative, Kahn—negative.

In this case the serologic reactions continued positive for a period of 18 days following the last chill.

It would then appear that if one allows a month to elapse following a malarial infection, the serologic reactions should certainly have become negative, assuming that adequate therapy has been given. In this regard it should be noted that all our cases were treated with the "long course" treatment of

quinine, i.e., daily quinine over a period of six to eight weeks. With the "short course" four day treatment as now advocated by some, the serologic changes to negativity may not be so rapid.

SUMMARY

1. Sixty-four cases of naturally occurring malaria were reviewed.

2. Two cases are cited in which a diagnosis of syphilis was erroneously made on serologic reactions found to be positive because of latent malarial infection. In each case development of clinical malaria occurred before antisyphilitic treatment was begun. It is believed that these two cases will at least partially help to disprove the present accepted belief that the symptomless malarial carrier state cannot produce false positive serologic reactions.

3. The longest period of positivity of serologic reactions with quinine therapy was 18 days after the last chill. This occurred in only one case. The other cases all had negative reactions within a period of 10 days following the last chill.

BIBLIOGRAPHY

1. MOORE, J. E., EAGLE, H., and MOHR, C. F.: Biologic false positive serologic tests for syphilis. A suggested method of approach to their clinical study, Jr. Am. Med. Assoc., 1940, cxv, 1602.
2. MOHR, C. F., MOORE, J. E., and EAGLE, H.: Biologic false positive serologic reactions in tests for syphilis. Occurrence with organic diseases other than syphilis, Arch. Int. Med., 1941, lxviii, 1161.
3. MOHR, C. F., MOORE, J. E., and EAGLE, H.: Biologic false positive serologic reactions in tests for syphilis. Occurrence in normal persons, Arch. Int. Med., 1941, lxviii, 898.
4. EAGLE, H.: On the specificity of serologic tests for syphilis as determined by 40,545 tests in a college student population, Am. Jr. Syph., Gonor., and Ven. Dis., 1941, xxv, 7.
5. KITCHEN, S. F., WEBB, E. L., and KUPPER, W. H.: The influence of malarial infections on the Wassermann and Kahn reactions, Jr. Am. Med. Assoc., 1939, cxii, 1443.
6. HAZEN, H. H., SENEAR, F. E., PARRAN, THOMAS, SANFORD, A. H., SIMPSON, W. M., and VONDERLEHR, R. A.: Serologic evidence of syphilis in malarial patients, Arch. Dermat. and Syph., 1938, xxxvii, 431; abstr. Jr. Am. Med. Assoc., 1938, cx, 1629.
7. WILSON, R., JR., and LEVIN, A. L.: Observations on effect of malaria on Wassermann reaction, Am. Jr. Med. Sci., 1936, cxci, 696.
8. NAGELL, H., and LANGHANS, J.: Impf. Malaria und Wassermannsche Reaktion, Med. Klin., 1928, xxiv, 368.

THROMBOSIS AND EMBOLISM OF THE ABDOMINAL AORTA *

By Irving Greenfield, M.D., F.A.C.P., *Brooklyn, N. Y.*

Thrombosis of the abdominal aorta was first described by Graham[1] in 1814. In the steadily growing literature, the diagnosis in the vast majority of cases has been confirmed by postmortem examination. The number of reported cases, however, gives a false index of the frequency with which thrombosis and embolism of the abdominal aorta occur. For, as Leriche[2] pointed out, a number of cases are not reported because recovery prevented confirmation of the diagnosis. It is reasonable to state, therefore, that thrombosis and embolism of the abdominal aorta probably occur more frequently than the proved reported cases would seem to indicate.

In 1898, when Welch[3] reviewed the literature, 59 cases were collected. Thrombosis of the abdominal aorta was suspected in 14 of these cases and an embolus in the remainder. Thirty-three additional case reports were added during the next 34 years, and to these Wylde[4] added two cases which he observed, bringing the total number of cases which he reviewed to 94. In an excellent summary of the literature, Banowitch and Ira[5] cited 11 additional cases and added five cases which they observed at the Long Island College Hospital. Rothstein[6] collected and reviewed briefly the reports of 13 cases of thrombosis and embolism of the abdominal aorta which occurred in infants and in children under 15 years of age. To these, his case was added, so that in 1935 the total number of recorded cases was 123. During the past seven years, 33 additional observations have appeared. This brings the total number of cases of thrombosis and embolism of the abdominal aorta reported during the century and a quarter which followed Graham's original description to 156. The purpose of this presentation is to add five additional cases. One of these was observed by the author; and the remaining four † were taken from the records of the Brooklyn Jewish Hospital.

CASE REPORTS

Case 1. A 56 year old white man who had had a right nephrectomy because of tuberculous disease was taken ill with pains in the right upper abdomen several hours after a meal consisting of waffles and butter. The pain was colicky in character, radiated to the right shoulder, and was associated with nausea and general malaise. Four days later a yellowish discoloration of the sclerae and skin was noted. The temperature was elevated to 102° F.; the systolic blood pressure in mm. of mercury was 126 and the diastolic 70. The pulse rate was 84 per min. Bed rest was advised.

The fever subsided and the icteric tint of the sclerae diminished. At about midnight on the tenth day of his illness, he complained of a "numb feeling" in both lower extremities associated with a desire to urinate. The patient left his bed and 10 minutes later was found lying on the bathroom floor complaining of agonizing pains in the region of the sacrum, the perineum and both lower extremities. He was carried back to bed in shock and was seen within the hour. His lips were pale. The respirations were rapid and shallow. There were frequent cries signifying intense pain. The pulse rate was 110 per min. The blood pressure in mm. of mercury was 120 systolic and 70 diastolic. The only pertinent positive physical finding aside from the lower extremities was a loud harsh systolic apical murmur. The lower limbs were warm but presented a cadaveric pallor. The pulsations of the major vessels of both extremities, though diminished, were present up to the groin. A large dose of pantopon was given to control the severe pain.. Because of the diminution of the peripheral pulsations bilaterally together with the intensity and distribution of the pain, a lesion at the bifurcation of the aorta was suspected. The pain was so severe that it was not controlled by pantopon and though the narcotic effect of the opiate was definite, slumber was interrupted by frequent groans which indicated that pain was still present. Within two hours the condition of the extremities had changed. The skin was cool and presented the appearance of cutis marmorata from the groin to the toes. The pulsation of the major vessels of both lower extremities from the dorsalis pedis to the femoral arteries had disappeared. Papaverine was given intravenously without effect. In spite of additional pantopon the patient continued to complain of agonizing pain in the perineum, over the sacrum and in both lower extremities.

On admission to the hospital four hours after the onset of the acute symptoms, the patient was in acute distress. His restlessness and frequent shouts of pain were relieved by the intravenous administration of amytal solution. Examination at this time revealed a rectal temperature of 97.6° F., pulse 125, respirations 32, and blood pressure in mm. of mercury 130 systolic and 95 diastolic. The cutis marmorata was a deep purple and extended from the toes to the lower abdominal wall, the scrotum and the buttocks. The skin of both lower extremities was cool from the groin to the toes. No pulsations in the major vessels of either lower extremity could be felt.

The laboratory data were: hemoglobin 79 per cent, red blood cells 4.0 m., white blood cells 13,800, polymorphonuclear leukocytes 96 per cent, lymphocytes 2 per cent, monocytes 2 per cent. The urine had a specific gravity of 1.022 and contained a considerable amount of protein, sugar and acetone. The blood sugar was 211 mg. per cent, urea 25.8 mg. per cent and carbon dioxide combining power 53 volumes per cent. Oscillometric readings taken at various levels from the foot to the groin failed to show patency of the vessels of either lower extremity.

The clinical impression was that of occlusion of the abdominal aorta at its bifurcation. After 16 hours both femoral arteries were opened. The vessel walls were found to be thickened and sclerotic. Cork screw platinum probes were introduced into the lumina of the vessels for a distance of several inches and withdrawn, but no thrombus or part of the thrombus or blood followed the removal of the probe. The vessels were closed and the wounds were sutured.

The patient was returned to his room and 5000 units of liquaemin* in normal saline were administered intravenously. The pulse was rapid and feeble. Râles were audible throughout both lung fields. The patchy cyanosis of the extremities was replaced by a diffuse cyanosis. The temperature rose to 105.8° F. The blood pressure in mm. of mercury was 90 systolic and 70 diastolic. His condition grew rapidly worse and death occurred 33 hours following the onset of the acute vascular attack.

The anatomic diagnoses were: arteriosclerosis generalis; myomalacia cordis; mural thrombus in the left ventricle; dilatation of the heart; thrombus in the ab-

* The liquaemin was supplied by Roche-Organon, Inc., Nutley, New Jersey.

dominal aorta, external and internal iliac arteries with occlusion; thrombi in branches of the pulmonary artery; infarcts in the lungs; focal bilateral pneumonia; and infarct of the left kidney.

The pertinent findings at autopsy were as follows. The heart weighed 290 gm. The anterior wall of the left ventricle in the region of the apex appeared to be bulging, and the overlying epicardium was dull. The foramen ovale was patent. There was a sharply demarcated, slightly elevated, bizarre-shaped area in the myocardium of the septum and left ventricle at the apex which measured 4 by 1.5 cm. and was surrounded by a bright red border. There were numerous irregularly shaped friable blood clots on the endocardium overlying this area. Numerous smaller blood clots which were firmly adherent to the wall were present in between the rather widely separated trabeculae carneae. Many soft, irregularly shaped yellow deposits were present in the ascending part of the aorta and in the aortic leaflet of the mitral valve. The coronary arteries were tortuous. Their walls were markedly thickened and the lumina were narrowed by the deposition of firm calcified material. A lumen of the anterior descending branch of the left coronary artery could hardly be made out.

The abdominal aorta (figure 1) as well as both external and internal iliac arteries

Fig. 1. The abdominal aorta (case 1) was occluded by the clot which extended into both iliac arteries.

were filled with a friable blood clot, which in places was attached firmly to the wall. It reached 9 cm. above the bifurcation to the level of the inferior mesenteric artery. The intima of the aorta contained numerous soft yellow plaques. The walls of the femoral arteries were markedly thickened. In a cross section of the abdominal aorta, the intima was thickened. The endothelial lining cells were missing in areas and these roughened surfaces were covered by irregular thrombotic masses. The adventitia was normal. In cross sections from the left iliac artery, the right iliac artery and right femoral artery, the microscopic picture was similar to that present in the aorta. Additional findings included infarction of the left kidney and the lungs.

Comment. Though the diagnosis of occlusion of the abdominal aorta was made, surgical intervention was not undertaken until 14 hours had elapsed. This time interval, as suggested by Fry [7] and emphasized by Ravdin and Wood,[8] proved to be too long. The history of the sequence of events preceding the onset of the catastrophic terminal illness was so atypical

as to be misleading. Therefore, the presence of myocardial infarction was not suspected. In the light of the postmortem findings, it was evident that the absorption of blood elements which followed the myocardial infarction was the explanation for the mild jaundice. In spite of the marked generalized arteriosclerosis, it was felt that an embolus rather than a thrombus occluded the lumen of the aorta. This was based upon the fact that the mural thrombus, which was found on the portion of the endocardium of the left ventricle whose blood supply came from the occluded anterior descending branch of the left coronary artery, had a rough, bright, friable surface over its lower portion. The 5,000 units of liquaemin employed were equivalent to 2.5 c.c. At the time of administration heparin was a comparatively new drug and dosage schedules were not well established. The amount used represented about 12.5 mg. of the sodium salt of heparin, whereas now in the average case a daily dose of 300 mg. or more is given. It is questionable, therefore, whether the amount of heparin used had any effect.

Case 2. A 78 year old white man with evidence of prostatism and a cough of long duration was seized with a sudden attack of pain in the right upper abdomen radiating to the angle of the right scapula. It was not associated with nausea or vomiting. Three days after the onset of this episode, a mass appeared in the right lumbar region. On aspiration, a purulent fluid which was sterile on culture was obtained.

The pertinent physical findings were: temperature 99.8° F., pulse 98, respirations 20, blood pressure in mm. of mercury 150 systolic and 100 diastolic. The patient was dehydrated and appeared chronically ill. The chest was emphysematous. The heart tones were distant and of poor muscular quality. Frequent extrasystoles were audible. The right flank was more prominent than the left.

Laboratory data: hemoglobin 62 per cent, red blood cells 2.89 m., white blood cells 2,900, polymorphonuclear leukocytes 37 per cent, band forms 15 per cent, lymphocytes 38 per cent, monocytes 2 per cent, and eosinophiles 5 per cent. The urine was normal. The blood sugar, urea and carbon dioxide combining power were normal. The erythrocyte sedimentation rate (Westergren method) was 63 mm. in 1 hour. An intravenous urogram revealed normal kidney function; a conventional teleroentgenogram revealed moderate cardiac enlargement. The electrocardiogram revealed left axis deviation and myocardial damage. The sternal marrow picture was not specific.

The patient developed ascites. The anemia and leukopenia became more pronounced. A paracentesis abdominalis yielded 5 liters of clear fluid in which no neoplastic cells were demonstrable. The course was steadily downward and death occurred 22 days after his admission to the hospital.

The anatomic diagnoses were miliary tuberculosis of the lymph nodes, the peritoneum, the spleen, the pleura, the lungs, and the liver; arteriosclerosis generalis; cardiac hypertrophy; myofibrosis cordis; thrombus in the aorta; abscess in the stomach; cholecystitis; and cholelithiasis.

The pertinent autopsy findings were as follows. The peritoneal cavity contained approximately 2000 c.c. of a clear greenish fluid. The omentum was thicker than usual. The peritoneal surfaces, including the omentum, visceral and parietal peritoneum, mesentery, serous coats of the bowel and peritoneal reflection of the diaphragm, were studded with discrete, gray-white firm plaques which measured up to 0.5 cm. in diameter, were slightly raised above the surface, and were difficult to cut. The right pleural cavity contained 450 c.c., and the left 250 c.c. of fluid similar to that found in the peritoneal cavity. The parietal pleura was studded with nodules similar to those described above but smaller in size.

The heart weighed 430 gm.   The lower part of the lumen of the left ventricle was occupied by an irregular, firm, gray-white substance which was adherent to the posterior wall of the ventricle and the interventricular septum.   When this substance was removed the underlying endocardium was gray-white in color and thinner than the remaining, unaffected wall.   The coronary ostia were patent.   The coronary vessels were markedly sclerotic and contained numerous atheromatous patches.   The ascending and descending aorta were the seat of numerous, large, calcific, atheromatous plaques many of which were ulcerated.   Five cm. distal to the orifices of the renal arteries there was a globular distention of the aorta (figure 2), the lumen of which was filled with a rubbery, gray-white mass which was adherent to the vessel wall.

FIG. 2.   The globular distention of the aorta distal to the orifices of the renal arteries was filled with a rubbery, gray-white mass which was adherent to the vessel wall.

The pulmonary vessels showed a moderate amount of sclerosis.   The stomach was not remarkable except for the presence of a small, soft, greenish-yellow nodule 0.4 cm. in diameter in the cardiac portion of the stomach.   On section, a thick, creamy, greenish-yellow fluid exuded.   Microscopic sections from both lungs, the spleen, the omentum, the tracheobronchial and mesenteric lymph nodes revealed these organs to be the seat of miliary tuberculosis.

Comment.   This patient had miliary tuberculosis involving the lymph nodes, peritoneum, pleura, lungs, liver and spleen.   The thrombus which was found in an aneurysm of the abdominal aorta formed on an arteriosclerotic plaque in the lumen of the aorta and incompletely occluded the vessel.   There were no symptoms during the life time of the patient which would have focused attention on the lesion in the aorta.   There was a mural thrombus found in the left ventricle at the site of an old occluded coronary artery, which was in no way responsible for the thrombus which was present in the aortic aneurysm.   A type III pneumococcus was grown in pure culture from the pus evacuated from the abscess which was found in the stomach wall.

Case 3.   A 43 year old white man, with a history of a duodenal ulcer and syphilis which had been adequately treated, was admitted following the sudden onset of pain in the epigastrium and vomiting.   The pertinent findings on physical examination

included: temperature 101.2° F., and blood pressure in mm. of mercury 198 systolic and 88 diastolic. The pupils reacted to light and accommodation. A soft low-pitched aortic diastolic murmur was audible at the right of the sternum. Abdominal rigidity which was most marked in the epigastrium was present.

Laboratory data: hemoglobin 107 per cent, red blood cells 5.1 m., white blood cells 17,500, polymorphonuclear leukocytes 90 per cent, band forms 22 per cent, lymphocytes 6 per cent, monocytes 4 per cent. The urine contained albumin, sugar, and acetone, and occasional white blood cells. The blood Wassermann and Kline tests were negative. The erythrocyte sedimentation rate and blood chemistry were normal. A flat plate of the abdomen revealed distention and fluid levels in the loops of the small intestine. There was no free gas under the diaphragm. The barium enema was normal. The barium meal showed an irregularity in the caliber of the small intestine. The conventional teleroentgenogram was normal.

Fecal vomiting was present on the second day. The hospital course was progressively downward. Universal abdominal rigidity developed. The temperature continued to rise and the terminal picture was that of peritonitis. Death occurred 14 days after his admission to the hospital.

The anatomic diagnoses were: volvulus of the small intestine with gangrene, peritonitis, bronchitis, pneumonia, arteriosclerosis generalis, aneurysm of the abdominal aorta with mural thrombus, thrombus in the aorta and common iliac arteries, hypertrophy and dilatation of the heart.

The pertinent autopsy findings were as follows. On opening the peritoneal cavity, air escaped. The peritoneal surface was covered by a plastic, gray-green exudate. There were many fibrous and fibrinous adhesions between the loops of intestine. The omentum was in its normal position. There were more than 1,000 c.c. of thick, creamy, gray-green pus in the peritoneal cavity. A collection of thick, gray-green exudate which bathed 40 cm. of completely necrotic and unattached small intestine was found behind the terminal portion of the ileum. The proximal and distal portions of this loop of ileum opened into the peritoneal cavity. The remainder of the intestinal tract showed nothing of note.

The heart weighed 430 gm. The walls of the coronary arteries were thickened; the intima of the thoracic aorta contained many soft and firm yellow plaques. Immediately above the origin of the renal vessels, the wall of the aorta bulged out. Attached to the intima in this pocket was a firm thrombus which extended downward beyond the bifurcation of the aorta into the iliac arteries. The microscopic picture of a section taken from the aorta was that of a syphilitic aortitis.

Comment. The volvulus of the small intestine which went on to gangrene formation with a fulminating peritonitis completely clouded the picture found in the aorta at necropsy. In spite of the negative serologic reactions, the microscopic appearance of the section taken from the aorta revealed that vessel to be the seat of a syphilitic aortitis. The thrombus formed in the aneurysm and extended beyond the bifurcation of the aorta into the iliac arteries. There were no localizing signs during the stormy terminal illness which would have suggested the diagnosis of occlusion of the aorta.

Case 4: A 67 year old white man who had a peptic ulcer noted increased difficulty in starting the urinary stream, voided small amounts of urine frequently, and complained of dysuria. Acute urinary retention developed and hospitalization was advised.

The pertinent physical findings were: temperature 99.2° F., pulse 108, respirations 22, and blood pressure in mm. of mercury 136 systolic and 88 diastolic. The thorax was deformed as a result of a marked scoliosis. The lungs presented evidence of

early congestive heart failure. The heart was normal in size. A soft systolic murmur was audible at the apex. There were bilateral inguinal herniae. On rectal examination the prostate gland was enlarged.

Laboratory data: hemoglobin 67 per cent, red blood cells 4 m., white blood cells 13,200, polymorphonuclear-leukocytes 70 per cent, lymphocytes 25 per cent, band forms 12 per cent, monocytes 2 per cent, eosinophiles 1 per cent. The urine and blood chemistry were normal. The erythrocyte sedimentation rate (Westergren method) was 30 mm. The Wassermann reaction was negative.

On the tenth day, the patient had a chill with an elevation of temperature to 102° F. The urine contained a trace of protein and many clumps of pus cells. Two days later, his blood pressure dropped to 76 mm. Hg systolic and 60 mm. diastolic, and the patient was drowsy. Showers of fine râles with impaired resonance were present at the base of the left lung. There was a leukocytosis of 30,000 with 90 per cent polymorphonuclear leukocytes. Roentgenographic examination confirmed the presence of bronchopneumonia. The electrocardiogram showed right axis deviation. Four days later a left facial palsy and weakness of the left hand were noted. The blood urea nitrogen was 53.5 mg. per cent. He became markedly dyspneic and cyanotic. The heart rate was extremely rapid. Generalized muscular twitchings developed, and the patient died on the twenty-first day after his admission to the hospital.

The anatomic diagnoses were: arteriosclerosis generalis; mural thrombus in the aorta, infarction of the kidneys; cardiac dilatation, atelectasis of the lung, stomach ulcer and argentaffin cell tumor of the jejunum.

The pertinent autopsy findings were as follows. The heart weighed 280 gm. The coronary arteries were opaque, firm, gray and tortuous. The aorta was the seat of marked sclerotic changes. The intima contained numerous raised, firm, yellow and gray sclerotic plaques. The elasticity was markedly impaired. A firm, brown blood clot was found adherent to and embedded in a slight outpouching (figure 3) of the

FIG. 3.   Photograph of the fixed specimen of the abdominal aorta in case 4 showing the contracted clot which was embedded in the outpouching of the aorta.

aorta 3 cm. above the bifurcation. The free surface of the thrombus completely occluded the lumen of the aorta. There were many nonperforating ulcers along the lesser curvature of the stomach near the pylorus. The bladder was the seat of an acute cystitis. The prostate gland was enlarged.

Comment. The mural thrombus which was found in the aorta had formed on a sclerotic plaque in the vessel wall. The presenting symptoms were those of urinary sepsis with renal failure. There was nothing in the history to suggest impaired circulation below the point of obstruction.

Case 5. A 41 year old white woman, with a history of intolerance to greasy and fried foods, had a recurrent attack of nausea, vomiting and belching. During this attack, which lasted three days, jaundice, constipation, and loss of appetite were noted.

The pertinent findings on physical examination were: temperature 101.9° F., pulse 110, respirations 22, blood pressure in mm. of mercury 150 systolic and 90 diastolic. The sclerae and skin were icteric. There were signs of congestion at the bases of both lungs. The liver was palpable four fingers' breadth below the costal edge.

Laboratory data: hemoglobin 67 per cent, red blood cells 3.89 m., white blood cells 18,600, polymorphonuclear leukocytes 78 per cent, lymphocytes 9 per cent, band cells 9 per cent, monocytes 4 per cent. The urine, aside from containing bile pigments, was normal. The erythrocyte sedimentation rate (Westergren method) was 35 mm. in 1 hr. The blood sugar and urea were normal. The total cholesterol was 218 mg. per cent; the free cholesterol was 127 mg. per cent; the cholesterol esters 58 mg. per cent; the phosphorus 2.2 mg. per cent; phosphatase 7.5 Bodansky units; the direct van den Bergh was positive and the indirect was 24.8 units. The stool contained bile.

Her course was progressively downward. The jaundice increased. The patient became confused mentally, developed signs of bronchopneumonia, and died after going into circulatory collapse on the seventh day after her admission to the hospital.

The anatomic diagnoses were yellow atrophy of the liver, cholemic nephrosis, dilatation of the heart and thrombosis of the aorta.

The pertinent autopsy findings were: the skin and sclerae were yellow. The heart weighed 245 gm. The coronary ostia and coronary arteries were patent. The elasticity of the aorta was not impaired. A thrombus which completely occluded the aorta was found adherent to the intima at the bifurcation. It extended into the common iliac arteries for a distance of 5 cm. The liver and spleen were both enlarged. The kidneys showed evidence of a cholemic nephrosis.

Comment. The thrombus found in the aorta was adherent to an area in the intima which was the seat of a calcified plaque. The terminal picture which was typical of an acute yellow atrophy of the liver completely obscured the presence of a thrombus in the aorta.

DISCUSSION

Thrombosis and embolism of the abdominal aorta are relatively infrequent catastrophies which occur in individuals with chronic vascular and chronic valvular disease. The rôle of the chemical, colloidal, and physical changes which take place in the blood, together with the rôle of injury to the endothelial cells of the intima and the rôle which stasis plays in the formation of thrombi, have been a matter for much speculation, a discussion of which is beyond the scope of this presentation. Though adequate studies of the factors which may increase the coagulability of the blood during the course of infectious diseases have not been made, Hunter [9] believed that occasionally thrombi resulted from the action of bacterial toxins on the endothelial cells of the intima. Manasci,[10] Bodeff,[11] Moschcowitz,[12] Wheeler,[13] and Rothstein [6] cited instances in which sudden occlusion of the abdominal aorta occurred during the course of infectious diseases. Retrograde thrombosis may occur and may extend upward to involve the aorta from a distant traumatized

vessel. Thrombosis may also occur in arteriosclerotic vessels (cases 2 and 4) or in an aorta which is the seat of chronic vascular disease such as thromboangiitis obliterans or syphilis (case 3). In the former, the thrombus may form on an atheromatous plaque or at the site of a roughened intima, whereas in the latter the occlusion is usually at the site of a chronic inflammatory process.

There are many sources from which emboli which occlude the abdominal aorta may take their origin. When disease of the heart is present, and particularly if such disease is associated with disturbances in rhythm, sudden occlusion of the aorta can usually be attributed to an embolus of central origin. In the presence of a patent foramen ovale, an embolus to the aorta may take its origin in either the right side of the heart or from the site of a thrombophlebitis. Rheumatic heart disease, chronic congestive failure, auricular fibrillation, myocardial infarction and coronary artery thrombosis are associated with a high incidence of mural thrombi. These thrombi, which may be flat or polypoid, are usually found in the recesses of the heart where the circulation is slowest. A portion of such a mural thrombus may become detached from its base and pass with the general blood stream to the point of arrest. Thrombi in the walls of the aorta may be responsible for emboli to some distant point. The ball valve thrombus of the auricle, which according to Garvin [14] is extremely rare, may also be the starting point for an embolus to the aorta.

Incidence. The relative infrequency with which the abnormality under discussion occurs may be judged by reviewing its incidence as reported from several hospitals. Thrombosis and embolism of the abdominal aorta were found but once in 1047 consecutive postmortem examinations made at the Research and Educational Hospitals of the University of Illinois.[15] Siegal and Garvin [16] found 11 cases of abdominal aorta thrombosis in their review of 6547 autopsies performed at the Cleveland City Hospital. Seven cases were found in a study of 5350 necropsies reviewed by Philips and Gross [17] at the Montefiore Hospital in New York City. The five cases reported in this communication represent the number found in 3991 consecutive autopsies performed at the Jewish Hospital of Brooklyn.

Distribution. Embolism of the abdominal aorta appears to occur with equal frequency among men and women, but the ratio of males to females who have thrombosis of the aorta is about 2 : 1. Thrombosis and embolism of the abdominal aorta occur at all ages. The earliest recorded case of thrombosis of the abdominal aorta was that of the 10 day old infant with an umbilical cord infection reported by Moschcowitz.[12] The majority of cases, however, have occurred in individuals in the fourth and fifth decades of life.

Symptoms. The most alarming aspect of the symptomatology of thrombosis and embolism of the abdominal aorta has been emphasized in dramatic language. In spite of the fact that the usual clinical picture is ushered in with symptoms which are sudden in their onset, the acute episode

has occasionally been overlooked because the characteristic pain as a major symptom has been absent.[18]

On the basis of the symptomatology, cases of abdominal aorta obstruction may be classified into two general groups, i.e., those in which the symptoms are slow in their onset and those in which the onset is sudden. The gradual onset of pain speaks in favor of a gradually narrowing process. In this group of patients a careful history may elicit evidence of intermittent claudication which is most often situated in the arch of the feet or in the calf muscles of the legs. If the occlusive arterial disease extends up as far as the femoral arteries, these symptoms may even be referred to the thighs or the hips. Color changes, disturbances of sensation and a gradually increasing coldness of the extremities may be present. A sudden change in this picture means the completion of the occlusion. In a thin individual, direct palpation may reveal absent pulsations of the abdominal aorta below the point of occlusion and occasionally dilatation of the aorta above the upper limit of the thrombus. With the onset of gangrene, the pain becomes constant and is severe. The extent of the gangrene will depend upon the completeness of the occlusion and the status of the collateral circulation.

In sharp contrast to the gradual progression of symptoms which perhaps occur more frequently with thrombosis is the sudden onset of agonizing pain usually referred to both lower extremities when the lesion is embolic. Occasionally the pain may be referred to the abdomen, the inner aspects of the thighs, the scrotum, the sacrum, the small of the back, the loin or the perineum. Sudden collapse accompanied by a cold and clammy perspiration may be followed by evidence of interference with the circulation of both lower extremities. The pain may be constant or paroxysmal. Coldness, numbness, pallor, and complete loss of sensation develop rapidly. Partial or complete paraplegia may be present. Cyanosis accompanied by mottling of the skin is often followed by gangrene. Pulsations of the major vessels of the lower extremities are altered and, depending upon the completeness of the occlusion, these pulsations may disappear promptly in both lower extremities or first in one extremity and then in the other. Urgency and frequency, vesical and rectal tenesmus, vomiting and diarrhea have been noted. Oscillometric readings from the dorsalis pedis artery to the femoral artery are either absent or are greatly diminished depending upon the completeness of the blockage. The skin surface temperature is definitely reduced. After a short interval gangrene develops, varying with the extent of the blockage and the state of the collateral circulation.

Differential Diagnosis. Though the classical syndrome may include the sudden onset of severe pain, loss of sensation in both lower extremities, absence of pulsations extending all the way up to include the femoral arteries, and a rapidly developing ascending gangrene with an ultimately fatal outcome, Philips and Gross [17] have reëmphasized the fact that this sequence of events is often not present. Widespread venous thrombosis of both lower

extremities has been mistaken for thrombosis of the abdominal aorta. In contradistinction to the coldness, pallor, loss of sensation and of arterial pulsations, absence of edema and the development of a dry gangrene in occlusion of the abdominal aorta, cases of venous thrombosis have warm, cyanotic, edematous extremities in which arterial pulsations may be identified depending upon the extent of the edema. Sensations are often unchanged and tender veins are usually present. If facilities are available, the intravenous use of a contrast substance for visualization of the vascular tree may be of differential diagnostic value.[2, 19]

Ischemic necrosis, occasionally seen in patients with advanced arteriosclerosis of the vessels of the lower extremities, should not be confused with the gangrene which develops following the dramatic onset of the vascular catastrophe under discussion. Simultaneous complete occlusion of both common iliac arteries may present a perplexing differential problem. Absent pulsations of the vessels of the lower extremities may occur in the presence of severe anemias, thromboarteriosclerotic disease of the vessels of the lower extremities, thromboangiitis obliterans, coarctation of the aorta, and extensive thrombophlebitis with reflex vascular spasm. Thickness of the skin in diseases such as scleroderma may interfere with the identification of main stem arterial pulsations of the vessels of the lower extremities. However, the patchy distribution of the skin lesions and the other stigmata of scleroderma should be of value. Functional circulatory disturbances are not likely to be confused with embolism.

Prognosis. The prognosis is always grave. Hess[20] showed that 95 per cent of the 73 cases which he collected died under conservative therapy. Rothstein[6] found that 112 patients or 91 per cent of the 123 reported up to 1935 proved fatal. Since then, 33 additional case reports have been added to the steadily growing literature. Of these, three patients were operated upon successfully and survived from six months to beyond three years. The total number of cases including those contained in this communication is now 161. Of these 147 or 91.3 per cent were fatal. Death occurred anywhere from within several hours to six months after the onset of symptoms. Those who live either develop an adequate collateral circulation without operative intervention or dislodge the embolus from the bifurcation of the aorta into one of the iliac arteries with resulting amputation of part of the extremity. A small number of patients recover following embolectomy with gangrene and partial amputation or following embolectomy without gangrene. Kerr's[21] patient survived embolectomy on two separate occasions and finally succumbed following an acute coronary artery occlusion.

Treatment. The diagnosis of occlusion of the aorta is not difficult when gangrene is obvious but treatment at that stage is futile. The diagnosis must be made early if treatment is to be of value. In the great majority of cases, occlusion of the abdominal aorta occurs in individuals with preexisting cardiac disease. The treatment, therefore, is sharply divided into two parts. The first is the treatment of the cardiac disease and the second is the treat-

ment of the aortic obstruction. Although the former is beyond the scope of this presentation, the latter may be either conservative or radical. The success of conservative therapy depends upon evidence of a progressively improving circulation. The decision as to whether to persist with conservative therapy depends upon evidence of a progressively improving circulation. Watchful waiting may offer as a reward the development of a sharply demarcated gangrenous area which may subsequently be treated surgically. Tingling of the toes after the appearance of numbness usually signifies returning blood supply and warrants the continuation of expectant treatment. Partially occlusive bandages, Buerger's exercises, the oscillating bed, tissue extracts, alcohol and papaverine may occasionally be used to advantage to promote the establishment of collateral circulation. Heparin has been used successfully by Ravdin and Wood[8] to prevent recurrence and distal propagation of the thrombus. If heparin is used, it is important to remember that the addition of minimal amounts of protamine will inactivate the heparin when one wishes to bring the coagulation time back to normal. Surgery should be employed early because changes in the intima at the site of the occlusion may form the starting point for additional thrombi despite the postoperative use of heparin. Delay in surgical intervention due to incorrect or hesitant diagnosis may necessitate partial amputation or may be responsible for a fatal termination. The surgical procedures employed include aortotomy and iliac or femoral arteriotomy with extraction of the clot. Resection of the occluded portion of the aorta together with lumbar sympathectomy have been performed. Paravertebral sympathetic block may be of value in relieving vascular spasm distal to the arterial obstruction.

SUMMARY

The classical syndrome of obstruction of the abdominal aorta is one which is sudden in its onset and has been associated with a well delineated group of symptoms including severe pain and loss of sensation in the lower extremities, absence of arterial pulsations, progressive ascending gangrene, and finally death. Five proved cases of occlusion of the aorta were studied. Four of the aortas were occluded as a result of a thrombus. In one case an embolus which had its origin in a mural thrombus was deposited at the bifurcation of the aorta and occluded it. All of the patients had evidence of generalized arteriosclerosis. In the case of the embolus, the mural thrombus formed on the wall of the ventricle in the portion of the muscle supplied by the occluded anterior descending branch of the left coronary artery. Three of the cases of thrombosis of the aorta occurred in men and one in a woman. The men were in a much higher age group, though all four cases occurred in individuals beyond the fourth decade of life. The classical uncomplicated clinical picture usually associated with complete occlusion of the abdominal aorta at its bifurcation was present only in the first case. Though thrombi which occluded the aorta were found at postmortem examination

in the remaining four cases, there was nothing in the clinical course to suggest involvement of the aorta.

CONCLUSION

1. A case of embolism of the abdominal aorta is reported.

2. The association of miliary tuberculosis, peritonitis, urinary sepsis and yellow atrophy of the liver with thrombosis of the abdominal aorta was noted.

3. Variations from the classical clinical syndrome of occlusion of the abdominal aorta were cited.

4. Five additional cases of occlusion of the abdominal aorta were added, making the total number of cases now on record 161.

BIBLIOGRAPHY

1. GRAHAM, R.: Case of obstructed aorta, Med. Chir. Trans. London, 1814, v, 297.
2. LERICHE, R.: Resection of the iliac-aortic bifurcation with bilateral lumbar sympathectomy in thrombosis of the aorta, Presse méd., 1940, xlviii, 601.
3. WELCH, H. W.: Embolism and thrombosis, Allbutt's System of Med., 1910, vi, 691–821.
4. WYLDE, C. O.: Embolism of abdominal aorta, Canad. Med. Assoc. Jr., 1922, xii, 647.
5. BANOWITCH, M. M., and IRA, G. H.: Embolism and thrombosis of the abdominal aorta. Report of 5 cases, Med. Clin. N. Am., 1928, xi, 973.
6. ROTHSTEIN, J. I: Embolism and thrombosis of the abdominal aorta in infancy and childhood, Am. Jr. Dis. Child., 1935, xlix, 1578.
7. FRY, F. W.: Embolism and thrombosis of the abdominal aorta, Modern Concepts of Cardiovascular Disease, 1940, ix, 5.
8. RAVDIN, I. S., and WOOD, F. C.: The successful removal of a saddle thrombus of the aorta, eleven days after acute coronary occlusion, Ann. Surg., 1941, cxiv, 834.
9. HUNTER, J.: A treatise on blood information and gun shot wounds, 1794, G. Nicoll, London.
10. MANASCI, R.: Aortic thrombosis complicating influenza, Riforma méd., 1927, xliii, 149.
11. BODEFF, D.: Abdominal aorta embolism complicating diphtheria, Monatschr. f. Kinderh., 1937, lxxi, 169.
12. MOSCHCOWITZ, E.: Thrombosis of aorta and both iliac arteries following streptococcus infection of the umbilical cord, Proc. New York Path. Soc., 1914, xiv, 21.
13. WHEELER, E. J.: Thrombosis of aorta and iliac vessels following pneumococcal infection of the umbilicus, Canad. Med. Assoc. Jr., 1921, xi, 532.
14. GARVIN, C. F.: Ball thrombi in the heart, Am. Heart Jr., 1941, xxi, 317.
15. LUETH, H. C.: Thrombosis of the abdominal aorta; a report of four cases showing the variability of symptoms, ANN. INT. MED., 1940, xiii, 1167.
16. SIEGAL, M. L., and GARVIN, C. F.: Thrombosis and embolism of the abdominal aorta, report of case with obstruction of renal arteries, Ohio State Med. Jr., 1941, xxxvii, 750.
17. GROSS, H., and PHILIPS, B.: Complete occlusion of the abdominal aorta, Am. Jr. Med. Sci., 1940 cc, 203.
18. NEUHOF, H.: Embolectomy with partial arterial occlusion from embolism of the extremities, Ann. Surg., 1932, xcvi, 44.
19. RECAGNO, J. C.: High thrombosis of the abdominal aorta, Rev. Latin Am., 1938, xxiii, 411.
20. HESS, E.: Über die Embolie und Thrombose der Aorta abdominalis und ihre operative Behandlung, Deutsch. Arch. f. klin. Chir., 1921, cxv, 812.
21. KERR, H. H.: Aortic embolectomy, Med. Ann. Dist. Columbia, 1935, ii, 249.

CASE REPORTS

CARCINOMA OF THE ISLANDS OF LANGERHANS WITH LIVER METASTASIS PRODUCING HYPERINSULINISM *

By J. S. BROWNING, M.D., *Indianapolis, Indiana*

THIS case is being reported because of the apparent rarity of the condition and the fairly typical clinical course exhibited. A review of the literature up to the time this paper was written revealed only 13 [1] similar cases reported in man, seven of which had either lymph node or liver metastasis or both. This patient presented the usual clinical picture associated with hyperinsulinism.[2] It is to be regretted that a biological assay for insulin was not made of the metastatic nodules in the liver, as has been shown by Powers and Wilder to be conclusive proof of the origin of these tumors. However, the pathological lesions and clinical symptoms in this patient were so typical that it is felt the diagnosis was evident.

CASE·REPORT

Clinical History. K. R., a white male, aged 36 years, a painter and decorator, was first seen January 20, 1937, because of frequent attacks of unconsciousness. The onset of his illness dated from August 15, 1936, following an alcoholic debauch on a hunting trip, during which he drank one to two pints of whiskey. On returning to his car, he lay down on the front seat where he lost consciousness for about two hours. Recovering spontaneously from this, he felt very weak and dizzy, but after eating, he felt normal. Two weeks later, after feeling perfectly well during the interim, he had another attack of unconsciousness without the antecedent alcoholic debauch. Subsequent attacks occurred every week or more. He could tell when these were coming on by a fluttering sensation in the abdomen. This sign, however, finally disappeared. Attacks usually occurred about 11:00 a.m. He never lost control of his sphincters. The attacks occurred more commonly after a period of physical effort but never after a period of rest. Usually he was able to walk to the house or car with a little help after the attack started and even then was able to swallow satisfactorily. This was usually followed by profuse diaphoresis. The only significant features of his past history were: an attack of polyarthritis at the age of eight, which kept him in bed for eight weeks; an accident at the age of 21 when he fell from the fourth floor of a building without losing consciousness; and another accident at the age of 35, when he fell off a porch onto his head, losing consciousness for only a few minutes. He had always been a somewhat heavy drinker.

Physical Examination. Temperature was 98.4° F., pulse 60–64, respirations 36, and blood pressure 110 mm. Hg systolic and 64 mm. diastolic. Otherwise routine physical examination and complete neurological examination were entirely normal.

Laboratory Findings. Urine was negative. Erythrocyte count was 4,700,000 with 14 grams hemoglobin (Newcomer); leukocyte count 9,050 with 74 per cent polymorphonuclears, 22 per cent small lymphocytes, 1 per cent monocytes, 2 per cent metamyelocytes and 1 per cent nonsegmented neutrophiles. The Kline and Kahn
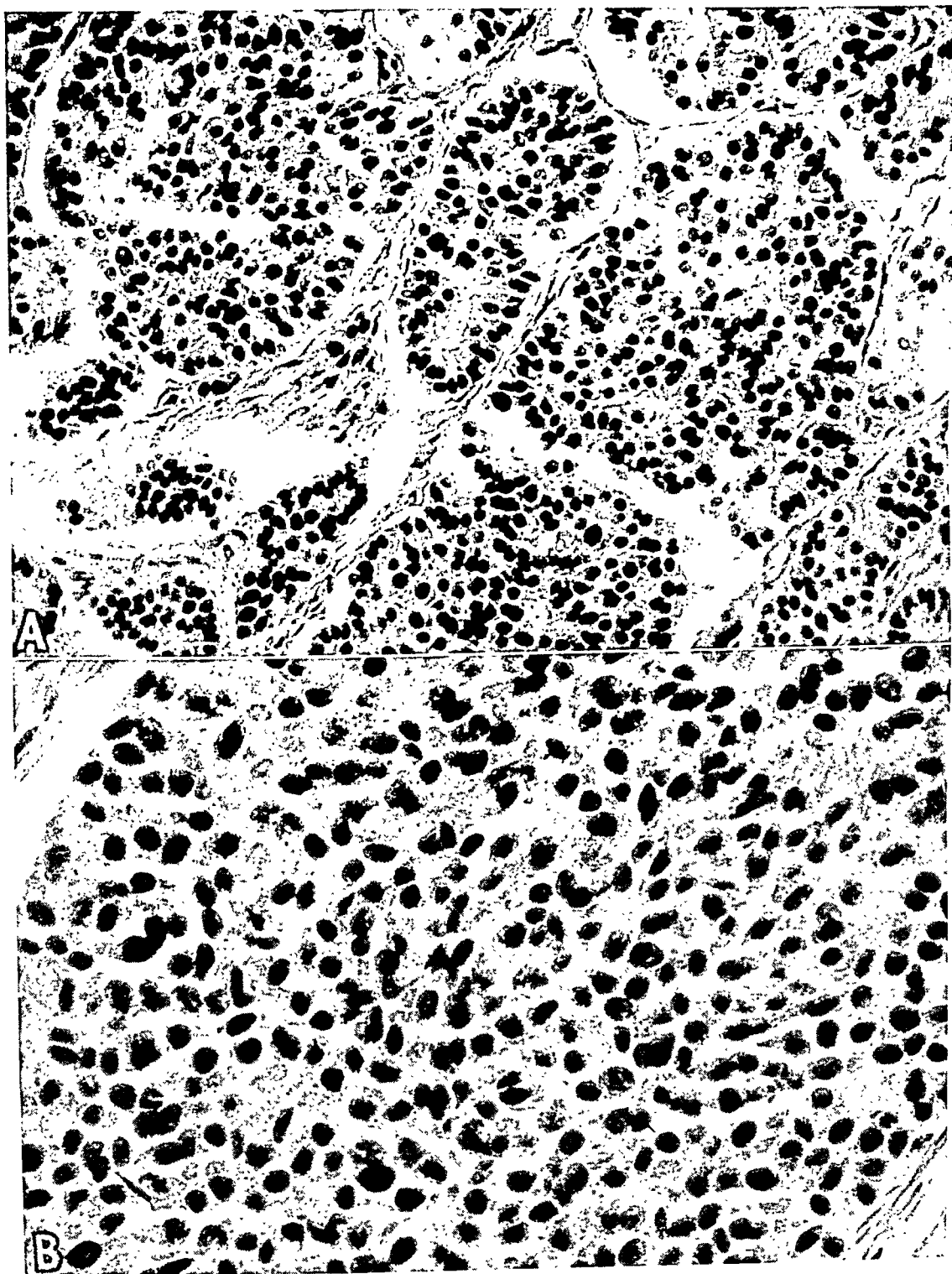
FIG. 1. (A) Section of tumor of pancreas.
(B) Section of lymph node adjacent to pancreas, showing metastasis.

tests were negative. Blood sugar on admission was 52 mg. per cent. Glucose tolerance test (100 grams of glucose by mouth) showed: fasting, 35 mg. per cent; one half hour, 104 mg. per cent; one hour, 121 mg. per cent; two hours, 106 mg. per cent; and three hours, 90 mg. per cent. Blood calcium was 10.4 mg. per cent. Spinal fluid examination on admission showed no cells, no globulin, and sugar 25 mg. per cent. Roentgenologic examination of chest and skull, and encephalogram were normal.

Clinical Course. The glucose tolerance test and the general characteristics of the attacks suggested the possibility of paroxysmal hypoglycemic reactions due to hyper-insulinism. He was requested to fast for a period of 24 hours. Within about 12 hours, however, he became unconscious, with generalized tonic and clonic convulsions and rather profuse diaphoresis. The blood sugar at this time was 18 mg. per cent. After 50 grams of glucose were administered intravenously, the patient rapidly regained consciousness and asked, "What happened?" This procedure was repeated with similar results. Repeated fasting blood sugar determinations were as follows: 35 mg. per cent, 48 mg. per cent, and 40 mg. per cent. He was maintained on a diet high in carbohydrate and protein, containing approximately 3,000 calories daily.

Exploration of the pancreatic tissue was deemed advisable in view of the following: (a) absence of any extrapancreatic causes of hypoglycemia, (b) repeated fasting blood sugars below 50 mg. per cent on an adequate diet, (c) several blood sugars below 40 mg. per cent which in some instances were associated with convulsive seizures that responded to the administration of glucose intravenously. On February 12, 1937, surgical exploration of the abdomen was performed revealing multiple small hard nodules in the pancreas which were interpreted by the surgeon to be due to inoperable carcinoma. There was one small metastatic nodule observed in the liver which was removed for biopsy (Section C). His operative convalescence was un-eventful, his hypoglycemic reactions being fairly well controlled by diet and intra-venous glucose. His course during the next year was rather stormy, requiring at least three admissions to the hospital for control of hypoglycemic reactions, in spite of attempted control at home with special diet and frequent feedings of sweetened orange juice when attacks occurred.

His last hospital admission was on April 8, 1938, because of a hypoglycemic reaction, in which the blood sugar was 12 mg. per cent. He responded to intra-venous glucose satisfactorily but while in the hospital developed scarlet fever and, in spite of intravenous scarlet fever antitoxin and other supportive therapy, died three days after the onset of scarlet fever with apparent circulatory failure and terminal pulmonary edema.

Necropsy. The chief findings at the postmortem examination were in the liver and pancreas. The pancreas weighed 174 grams. There was a nodular tumor mass, measuring 9 cm. in diameter, occupying the body of the pancreas and displacing the tissue in the proximal portion. The tail of the pancreas was diffusely infiltrated with tumor tissue and no recognizable normal pancreatic tissue remained. The proximal portion of the head of the pancreas appeared normal. The distal portion of the head was infiltrated by tumor tissue. In all a nodule of pancreatic tissue measuring about 4 cm. in diameter had a relatively normal appearance. Some of the adjacent nodes were greatly enlarged. The tumor tissue was of a firm consistency with a whit-ish homogeneous appearance.

The liver weighed 3,235 grams. The surface was smooth, but just beneath the surface were many irregular yellowish tumor nodules, measuring up to 4.5 cm. in diameter. On the cut surface the tumor nodules were found to be firm, with a faintly lobulated appearance. On section the largest nodule of the tumor tissue measured 8 cm. in diameter. Approximately two-thirds of the liver parenchyma was displaced by tumor tissue. The tumor nodules had a spherical contour with pinkish color. Some of the nodules showed scattered hemorrhagic areas.

The microscopic study of the tumor tissue of the pancreas (Section A) showed an atypical pattern with but few features of the normal gland. The tumor cells occurred in more or less compact masses varying greatly in size. The coarser masses were more numerous. Narrow, loosely organized connective tissue trabeculae separated the masses of tumor tissue. In none of these areas of tumor cells was there a definite acinar pattern. The cells were irregular in size and shape, and numerous atypical mitotic figures were found. Most of the nuclei were pyknotic and deep staining. The morphology of these cells and masses of tissue had all the characteristics of cells described in previous reports,[1] said to have had their origin from islet cells and shown by biologic assay to contain insulin. The cells in the lymph node adjacent to the pancreas (Section B) presented the same histological features. The enlarged photomicrograph (Section B) clearly demonstrates the cytology of
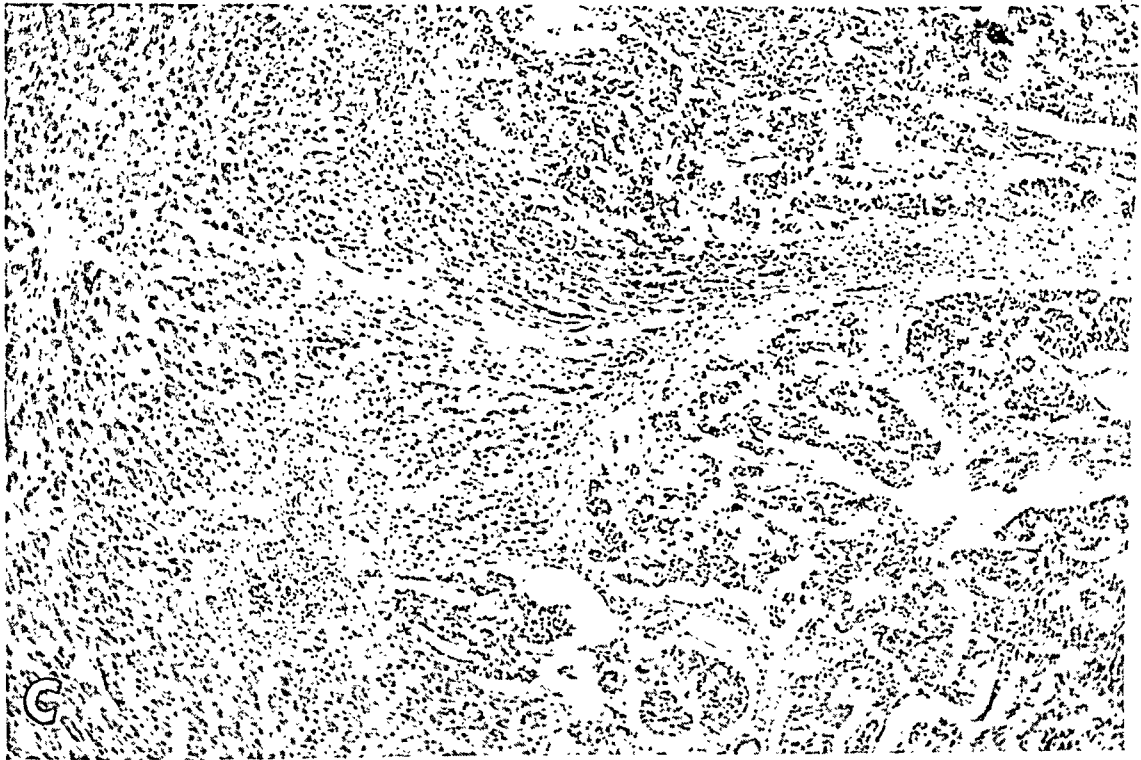
FIG. 1. (C) Section of metastatic nodule in liver removed at operation.

the tumor tissue. The metastatic nodules in the liver (Section C) had the same histologic structure as those in the pancreas and lymph node. Along the margins of the masses of tumor cells cord-like strands extended into the liver parenchyma. The cytoplasm of the tumor cells in both the pancreas and liver was very acidophilic. In no area were there any cell arrangements resembling acini or glandular structures, but rather they occurred in masses as described in the pancreas.

COMMENT

It is interesting that this patient could survive approximately 14 months after a positive diagnosis of inoperable metastatic islet cell carcinoma had been made. His hypoglycemic reactions were severe but were responsive to early treatment with glucose intravenously or sugar by mouth. One wonders whether an oper-

able tumor might have been found, as in a few previously reported cases, if this patient had presented himself when his symptoms first appeared.

I wish to thank Dr. J. O. Ritchey, Professor of Medicine, Indiana University School of Medicine, for certain notes and suggestions; also Drs. F. C. Forry, Professor of Pathology, Indiana University School of Medicine, and H. C. Thornton, Pathologist, Indianapolis City Hospital, for their pathological interpretations, used in this case report.

BIBLIOGRAPHY

1. WILDER, R. M., ALLAN, F. N., POWER, M. H., and ROBERTSON, H. E.: Carcinoma of the islands of the pancreas; hyperinsulinism and hypoglycemia, Jr. Am. Med. Assoc., 1927, xxcix, 348–355.

   THALHIMER, WM., and MURPHY, F. D.: Carcinoma of the islands of the pancreas; hyperinsulinism and hypoglycemia, Jr. Am. Med. Assoc., 1928, xci, 89–91.

   HOWLAND, G., CAMPBELL, W. R., MALTBY, E. J., and ROBINSON, W. L.: Dysinsulinism, Jr. Am. Med. Assoc., 1929, xciii, 674–679.

   HAMDI, H.: Ein insulargenetisches Pankreascarcinom (Insulom), Ztschr. f. Krebsforsch., 1932, xxxvii, 411–413.

   CALLALORDA, J., ESCARRAS: Epithelioma of Islands of Langerhans, Lyon chir., 1933, xxx, 248–253.

   JUDD, E. S., FAUST, L. S., and DIXON, R. K.: Carcinoma of the islands of Langerhans with metastasis to the liver producing hyperinsulinism, West Jr. Surg., 1934, xl, 555–557.

   BICKEL, G., MOZER, J. J., and JUNET, R.: Diabete avec dénutrition grave: Disparition de la glycosurie et atténuation progressive de l'hyperglycemie à la suite du développement d'un carcinome insularie du pancréas avec métastases hépatiques massives, Bull. et mém. Soc. méd. d. hôp. de Paris, 1935, li, 12–21.

   EVANGELISTI, T.: Cancer with cells of islet type, carcinoma of endocrine type, Policlinico (sez. chir.), 1935, xlii, 384–403.

   CRAGG, R. W., POWER, M. H., and LINDEN, M. C.: Carcinoma of the islands of Langerhans with hypoglycemia and hyperinsulinism, Arch. Int. Med., 1937, lx, 88–99.

   JOACHIM, H., and BANOWITCH, M. M.: A case of carcinoma of the islands of Langerhans with hypoglycemia, ANN. INT. MED., 1938, xi, 1754–1759.

   ISAJI, M.: Uber Inselzelladenome und Inselzellcarcinome der Bauchspeicheldrüse, Frankfurter Ztschr. f. Path., 1939, liii, 178–207.

   FLINN, LEWIS B., BEATTY, G. A., GINSBERG, MILTON, and HEMSATH, F. A.: Carcinoma of the Islands of Langerhans, Jr. Am. Med. Assoc., 1941, cxvii, 283–285.

   BALLINGER, JOSEPH: Hypoglycemia from metastasizing insular carcinoma of aberrant pancreatic tissue in the liver, Arch. Path., 1941, xxxii, 277–285.

2. HARRIS, SEALE: Hyperinsulinism and dysinsulinism, Jr. Am. Med. Assoc., 1924, xxciii, 729–733.

CHRONIC HEMOLYTIC ANEMIA WITH AUTOAGGLUTINATION AND HYPERGLOBULINEMIA; REPORT OF A FATAL CASE *

By ROY R. KRACKE, M.D., and BYRON J. HOFFMAN, M.D.,

Emory University, Georgia

THE presence of any intravascular mechanism that destroys red cells in excess of bone marrow compensation results in an anemia of the hemolytic type.

Any classification of the hemolytic anemias is difficult because of the large number and wide variety of agents that can destroy red cells. Among such agents are bacterial and parasitic infections, drugs, chemicals, animal poisons, and occasionally red cell destruction occurs as an allergic phenomenon as observed in sensitivity to the bean *Vicia fava* or the pollen of its flower. Chronic familial hemolytic icterus with spherocytosis, increased fragility of the red cells to hypotonic saline solutions and subsequent clinical cure by splenectomy is one of the more common types of hemolytic anemia in which the mechanism of hemolysis remains unknown.

The case reported in this paper is one of long standing, severe intravascular red cell destruction accompanied by reticulocytosis, numerous erythroblastic crises, splenomegaly, auto-agglutination and hyperglobulinemia. The cardinal features in this patient included a high amount of globulin in the blood from an unknown cause, accompanied by strong agglutination of her own cells as well as the cells of members of all blood groups. After many years of marked compensatory erythropoietic activity as indicated by reticulocytosis, her bone marrow became unable to compensate, and finally death occurred. We are unable to find an instance in the medical literature presenting the same features as seen in this patient.

The terms encountered in the medical literature denoting auto-agglutination are numerous and somewhat contradictory. Landsteiner was the first to distinguish clearly between *pseudo-agglutination* and *auto-agglutination*. His classification differentiates these conditions accurately and he distinguishes carefully between *pseudo-agglutination, cold (auto) agglutination,* and *iso-agglutination.*

Pseudo-agglutination may be designated as that condition in which there are varying degrees of rouleaux formation without subsequent hemolysis, which can be dispersed by agitation of the cell mixture. Errors in the determination of blood groups occasionally occur because of excessive rouleaux formation, and if this is marked it may simulate a true agglutination. It is most often seen in acute infections and is thought by some workers to be caused by increased viscosity of the blood serum.[3, 5, 6, 7] Slight dilution, as little as 1:3, dissipates this pseudo-agglutination. True iso-agglutination is not affected by agitation. The active principle in rouleaux is not absorbable, operates much more strongly at body temperature, is inactivated by dilution, and is non-specific. Cold agglutinins, on the other hand, become active at lowered temperatures and agglutinate the red cells of the same type and the same individual. For this reason these agglutinins have also been called auto-agglutinins. They are absorbable, withstand considerable dilution, and are non-specific.

Iso-agglutinins of human sera form the basis of determining the individual blood groups. When these agglutinins are mixed with cells containing the same agglutinogen, marked agglutination follows. They are called iso-agglutinins because of their specific action on blood cells of a subject of the same species. These iso-agglutinins are absorbable, are little affected by temperature change, withstand considerable dilution without becoming inactive, and indicate a specific blood group.

Reimann[3] first called attention to the "auto-hemagglutination" present in the blood of a patient being treated for arthritis. He observed that the red cells

of this patient underwent marked rouleaux formation on ordinary smears, in the red cell pipette and in the counting chamber when Hayem's solution was used as a diluent. This rouleaux formation led him to question the diagnosis of arthritis, and suspect hyperproteinemia secondary to multiple myeloma which was subsequently proved to be correct at necropsy. This rouleaux formation in his case was pseudo-agglutination instead of true auto-agglutination in the light of Landsteiner's classification. Jacobson [4] observed similar difficulties using Hayem's solution and determined that the precipitated substance belonged to the euglobulin portion of the blood protein and that euglobulin was precipitated by the bichloride of mercury which is one of the ingredients of Hayem's solution. Bonniger [5] reported similar observations but found no clumping of cells when salt solution was used as a cell diluent. Reimann,[3] Bonniger,[5] and Magnus-Levy [7] attribute the marked rouleaux formation to increased blood globulin and fibrinogen in their cases of multiple myeloma.

Antopol [8] and associates reported two cases of acute hemolytic anemia following neoprontosil therapy. Both of these patients were found to have blood of type O prior to the administration of the drug. After administration of the drug the first patient developed anemia, jaundice, and hematuria. The unwashed red cells were agglutinated by the patient's own serum and also the serum of groups A, B and O. This agglutination disappeared, however, when the preparation was heated to 37° C. The second patient also developed anemia and jaundice, and the serum agglutinated the patient's cells and other type O cells at room temperature, but the agglutination disappeared after incubation at 37° C. This appears to be an instance of cold agglutinins with corresponding hemolysins which became active after sulfanilamide therapy.

Hyperproteinemia has been observed in many chronic infections such as syphilis,[9] tuberculosis,[10] trypanosomiasis,[11] filariasis,[12] schistosomiasis,[13] sarcoid of Boeck,[14] lymphogranuloma,[15] kala-azar,[16] and multiple myelomatosis,[6] malignant tumors of the kidney,[17] and in lymphosarcoma.[18] In only one instance has it been reported in hemolytic jaundice,[19] and this was an "unexplained case" reported by Jeghers and Selesnick in which the total protein was 8.6 grams per 100 c.c. of blood with a globulin value of 4.5 grams and albumin of 4.1 grams.

CASE REPORT

The patient was a white female, married, aged 32. She was admitted to the Emory University Hospital on January 16, 1940 with a chief complaint of weakness, and a prolonged history of a "peculiar" anemia that had been studied in many clinics with a variety of diagnoses.

Past History and Present Illness. Her childhood diseases included measles, mumps, chicken pox, and whooping cough without complications. The patient had always been well and had led a normal active life until the autumn of 1934. At that time she developed a mild fleeting arthritis involving the elbow, wrist, ankle, and finger joints, which never remained over 24 hours at one time. The involved joint would be painful on motion, slightly swollen, but never hot to palpation. She had had frequent upper respiratory infections during the winter, and had pneumonia during February of 1935 with a weight loss of five pounds. There were no further difficulties until August 1935, at which time weakness and fatigue on walking slowly developed and became progressively severe. She went to a sanatorium in England in September 1935 to gain strength, received symptomatic treatment, and was dismissed in November

as improved. Again in December 1935 there was an exacerbation of weakness and dyspnea on exertion. Constant bed rest was necessary because of weakness. She gradually improved, had an uneventful winter, developed pneumonia again in June 1936 and was brought to a New Haven, Connecticut, hospital. Here she was found to have a severe anemia accompanied by hepatomegaly and splenomegaly but no definite diagnosis was made. Gastric analysis at that time revealed free HCl. She improved after several weeks' rest, but had another relapse of weakness at which time a diagnosis of acute hemolytic anemia of Lederer was made. A transfusion was given but this was followed by chills, fever, and very dark urine. Radiation of the spleen was begun but discontinued because of a severe reaction. At this time a mild icterus was noted for the first time. A remission occurred after several weeks. She was dismissed from the hospital in March 1937, but continued to have weakness and symptoms referable to anemia along with a mild fleeting arthritis. At this time she had returned to England where transfusions were given on repeated occasions without improvement in the state of anemia. Absolute bed rest for a period of several weeks seemed the most effective way to bring about improvement. Another severe relapse occurred in May 1939 and a mild icterus was noted. She was then transfused four times with severe reactions following the last two. She gradually improved after a few weeks and had several months of good health. She then came to Miami, Florida, for the winter and had another relapse in November. A transfusion given there because of the severe anemia was followed by a severe reaction accompanied by oliguria, coma, and an elevation of the non-protein nitrogen of the blood to 150 mg. per cent. After several weeks she slowly improved and was brought to the Emory University Hospital in January 1940. She and her husband stated that each relapse was usually accompanied by a sustained elevation in temperature of one to two degrees F. and that a temperature of 99° to 99.4° F. was not infrequent during remissions. *Positive Wassermann, Kahn, Kline and Eagle tests had been obtained on repeated occasions.*

System Review. The patient had had almost constant bronchitis since 1938 and dyspnea as described above. Her appetite was always good. She had no nausea, vomiting, or stool abnormalities. She had had mild jaundice with exacerbations of weakness as mentioned above. After transfusions the urine was noticed to be very dark yellow but never red or black. She noticed tingling in bottom of feet only once and this was during the relapse of 1936. Her skin had gradually become darker since 1936 and appeared to be a sun tan.

Family History. Her mother was living and well. *Her father was a native of Greece.* The patient had an *identical twin sister* who had always been well but who had also been found to have *positive Wassermann, Kline, Kahn, and Eagle reactions.* No form of antisyphilitic therapy was ever given the twin sister who has not been available to us for study. The mother had remarried and later had three boys who were all living and well.

Marital History. She had been married 11 years and had one son 10 years old who was apparently normal. She had had several miscarriages but only one since 1934 which was in 1939 during a severe relapse of anemia.

Menstrual History. Her menstrual periods began at 13 years of age, occurred at 28 day intervals, and were normal in amount, lasting from three to four days except during periods of severe anemia, at which time the amount would be scanty.

Drugs. She had had numerous courses of intramuscular injections of liver, iron by mouth, aspirin for arthritis and various placebos. No drugs had been taken without the advice of physicians. Several intensive courses of bismuth intramuscularly and iodides by mouth had been administered without noticeable improvement during the course of her illness.

Physical Examination. On physical examination she had the appearance of a

person about 40 years of age. Temperature was 99.1° F. The pulse was 76 and respiration normal. Blood pressure was 100 mm. Hg systolic and 70 mm. diastolic. The positive findings were confined to *splenomegaly, hepatomegaly,* and a *bronzing of the skin.* The spleen was palpable in the left side of the abdomen, moved on respiration, and extended 9 cm. below the left costal margin. The upper border of hepatic dullness began at the level of the fifth rib in the nipple line and extended inferiorly 13 cm. The lower edge was palpable and smooth. The bronzing of the skin involved the *entire body* and was similar in intensity to a good sun tan. All of the reflexes were physiological. Lymphadenopathy was confined to enlargement of the right submaxillary lymph node which was 1 cm. in diameter.

Laboratory Findings. Erythrocytes—3,780,000 per cu. mm. (Erythrocyte count was impossible with Hayem's diluting fluid because of marked clumping of cells. A slight amount was present when normal saline was used.) Hemoglobin—12 grams (Photoelectric). Leukocyte count—12,250. Differential: Mature segmented, 51 per cent; bands, 14 per cent; juveniles, 1 per cent; myelocytes, 2 per cent; plasma cells, 1 per cent; eosinophiles, 10 per cent; lymphocytes, 10 per cent; monocytes, 10 per cent; basophiles, 1 per cent.

A study of the blood film revealed numerous platelets, a moderate variation in the size of red cells, an occasional one being macrocytic, but most of the larger ones were normocytic with a considerable number of microcytic and well stained cells suggesting a possible spherocytosis.

Platelet count, 300,000 to 400,000; color index, 1.05; volume of packed cells, 37 per cent; volume index, 1.24; reticulocytes, 4.5 per cent; Price-Jones curve, average cell diameter 7.4 μ; icterus index, 5.0; van den Bergh, indirect, bilirubin content low. Kahn, 2 + to 3 + in various laboratories. Wassermann negative to 2 + in various laboratories. Fragility test: Patient—Hemolysis began at .46 per cent and was complete at .36 per cent NaCl solution. Control—Hemolysis began at .44 per cent and was complete at .34 per cent NaCl solution. Coagulation time five minutes. Donath-Landsteiner reaction negative. Heterophile agglutination positive through 1:8 dilution. Formol-gel reaction positive. Sedimentation rate (Wintrobe tube) 60 mm. in one hour.

As the red cells settled macroscopic clumping occurred. Gross clumping of the erythrocytes occurred within three to five minutes after being put in oxalate and citrate anticoagulants. No filaria were found in examinations of the peripheral blood at night. Her blood belonged to group O. For detailed results of crossmatching with various group O bloods see chart 1. If the clot was left in the serum for 12 hours no clumping occurred in the preparations of patient's serum and donor's cells and much less clumping occurred in the mixtures of the patient's cells with the patient's serum. When the clot remained in the serum for 24 to 36 hours very little to no clumping occurred in the preparations of patient's serum and patient's cells at room, ice box or body temperature, thereby indicating the absorbability of these auto-agglutinins.

Total protein (serum) 9.14 grams per 100 c.c.; albumin 3.78 grams per 100 c.c.; globulin 5.36 grams per 100 c.c.; A–G ratio 0.7 to 1. Spectroscopic examination of blood revealed no abnormal absorption bands.

Urine analysis: Albumin, negative; sugar, negative; acetone, negative; microscopic: occasional hyaline cast. Concentration test: concentrated to 1.020. Urea clearance, 103 per cent. Urobilinogen, not increased. Spectroscopic examination gave no abnormal bands.

Roentgenograms: Chest showed no abnormal findings. Skull and hands were negative for findings suggestive of Mediterranean anemia or multiple myeloma.

A skin biopsy was done and was negative for hemosiderin.

An hereditary anemia of the Mediterranean type seemed unlikely as the patient was so old when the erythroblastic crises developed and the bone changes characteristic

CHART I

Effects of Temperature on Cell Mixtures

	Room Temperature				
	30 Minutes	1 Hour	1½ Hours	2 Hours	12 Hours
Patient's serum with donor's* cells**	Negative	Negative	Occasional small clump, remainder of cells separate	Same as 1½ hours	Same as 1½ hours
Donor's serum with patient's cells**	Negative	Negative	Negative	Negative	Negative
Patient's serum with patient's cells**	Slight generalized clumping	Definite clumping	Definite clumping	Marked clumping	Marked clumping with fewer cells

	Ice Box—42° F.				
Patient's serum with donor's cells**	Negative	Very occ. small clump. Remainder of cells well separated	Same as 1 hr.	Same as 1 hr.	Same as 1 hr. Slight decrease in number of cells
Donor's serum with patient's cells**	Negative	Negative	Negative	Negative	Negative
Patient's serum with patient's cells**	Some generalized clumping, slightly more than at room temperature	Definite clumping	Marked clumping	Marked clumping	Marked clumping but few cells present

	Incubation—98° F.				
Patient's serum with donor's cells**	Negative	Tendency of some cells to group but not crowd together	Same tendency. More marked	Same as 1½ hours.	Occasional definite clumping with remainder of cells drifting
Donor's serum with patient's cells**	Negative	Negative	Negative	Negative	Negative
Patient's serum with patient's cells**	Slight tendency to clumping	Few small clumps	Marked amount of clumping	Definite clumping	Definite clumping. Fewer cells present. About same as 42° F.

    * Donor is any group O used.
    ** Cell suspension of 6 drops of whole blood to 5 c.c. of normal saline.

of this condition were not present. Abnormal auto-hemolysins due to congenital syphilis were considered but thought unlikely because former courses of antisyphilitic treatment had not proved beneficial. In addition her mother had always been well, had had no miscarriages, and had borne three normal children, now living and well, by a second husband. Furthermore the Donath-Landsteiner reaction was negative.

The presence of an enlarged liver and spleen accompanied by an anemia characterized by exacerbations and remissions, with varying degrees of reticulocytosis in an individual having a twin sister with the same type of serological reactions to the syphilitic antigen seemed to indicate a diagnosis of atypical familial hemolytic icterus in remission and splenectomy was considered. The positive serologic reaction was regarded as that which might accompany any condition having marked reticulo-endothelial proliferation, regardless of the etiology, as seen in malaria, infectious mononucleosis, etc.

Course. The erythrocyte count began to decrease steadily. On January 19 it was 3,600,000 with 6 per cent reticulocytes; on the 20th 3,450,000 with 6 per cent reticulocytes, and on the 21st, 3,300,000 with 6 per cent reticulocytes. An impending relapse was feared and splenectomy was performed on January 23, 1940, without operative difficulties or complications. Red cell counts before, during, and after splenectomy were constant. The spleen weighed 617 grams, was without perisplenic adhesions, and possessed a red, firm cut surface with prominent fibrous septa. On microscopic study the essential features were confined to an extensive and marked hyperplasia of the reticulum and lymphoid elements with some increase in fibrous tissue among the reticular elements and marked engorgement of the sinusoids with red cells. On January 25 the red cell count rose to 3,920,000 with 8 per cent reticulocytes. Bronchopneumonia developed in the left lower lobe and was treated with 15 grains of sulfapyridine each four hours. Twenty hours after the onset of sulfapyridine therapy the red cell count was found to be 1,900,000 and the reticulocyte count 9 per cent. The drug was discontinued, and on January 27 the red cell count was 2,470,000 with 9 per cent reticulocytes.

A transfusion with whole blood was not attempted because of the severe reactions that had always followed these and the renal failure that had accompanied well matched blood on former occasions. The bronchopneumonia gradually improved and the red cell count remained about 2,000,000 until February 14, when it rose to 2,600,000 per cu. mm. Reticulocytes varied from 10 to 20 per cent during this time. From one to two normoblasts per 100 white cells were present. The leukocyte count remained about 10,000 per cu. mm. with immaturity to the myelocytic stage in some of the cells. *Repeated blood Kahn and Wassermann reactions were negative two weeks after splenectomy.* The disappearance of the positive Kahn reaction following splenectomy seemed further to substantiate the probability of previous false positive tests from reticuloendothelial proliferation, regardless of the etiology.

The site of the operative lesion healed without complications. The red cells were slow to return to higher levels but by March 4 had reached 3,000,000 per cu. mm. and the patient was allowed to return home. During May the red cells reached 3,500,000 per cu. mm. and the patient was without complaints.

In June while in her summer home in Maine, a relapse occurred with an erythroblastic crisis, and she returned to the Emory University Hospital. The red cell count fell to 1,700,000, reticulocytes rose to 45 per cent and 100 nucleated red cells were present to each 100 leukocytes. The blood serum and urine were negative for hematoporphyrin or other abnormal absorption bands by spectroscopic studies. The Wassermann and Kahn reactions continued negative. At this time the icterus index was 18, the bilirubin was 3.2 mg. per cent with an indirect Van den Bergh reaction, and the urobilinogen content of the urine slightly increased. Serum protein studies showed a total protein of 9.48 grams, albumin of 4.15 grams and globulin of 5.33 grams per 100 c.c. Antisyphilitic therapy in the form of potassium iodide and weekly injections of bismuth was instituted for several weeks without improvement. As a last desperate therapeutic possibility 10 grams of gum acacia were administered intravenously as a 6 per cent solution in normal saline in an attempt to lower the blood proteins, particularly the globulin portion. Serum protein studies taken three days

later revealed the lowest protein values found during the entire period the patient was under observation. The serum albumin was 3.75 gm., and globulin 4.00 gm., with a total protein value of 7.75 gm. (chart 2). The Greenberg method of determining serum proteins was used and the total protein values checked by means of the falling drop densiometer.

Her final relapse, in the form of an erythroblastic crisis, continued with the degree of anemia becoming more severe and without a detectable decrease in the titer of the auto-agglutinins. The red cells fell to 1,200,000 per cu. mm. with 58 per cent reticulocytes. Air hunger became marked and was partially relieved for a short time by the use of an oxygen tent. Five hundred c.c. of citrated blood of Group O which showed the best preparations when "cross-matched" with the patient were given slowly without reaction or improvement. The erythrocyte count dropped to 900,000, air hunger became marked, and a terminal coma followed.

Postmortem Examination. Only a small incision of the abdomen was made, since consent for a complete examination could not be obtained. The liver was large, weighing approximately 2000 grams and extending 8 cm. below the costal margin in the nipple line. The surface was smooth and on cut section pale and slightly greasy to palpation. There was no abdominal lymphadenopathy. The kidneys were pal-

CHART II

Date	Total Serum Protein	Albumin	Globulin	A-G Ratio
2–16–40	9.14 grams	3.78 grams ·	5.36 grams	1 : 1.4
7–25–40	9.48 grams	4.15 grams	5.33 grams	1 : 1.28
8– 9–40	10.66 grams	4.71 grams	5.95 grams	1 : 1.26
8–11–40	10 grams of acacia as 10 per cent solution in normal saline.			
8–14–40	7.75 grams	3.75 grams	4.00 grams	1 : 1.06 ·

pated and normal in size. No abnormalities of the abdominal cavity were made out by palpation. The thoracic cavity was not entered.

On microscopic examination the kidneys were normal. There was no evidence of vascular disease, glomerulonephritis, or plugging of the tubules with hemoglobin crystals. The epithelial cells of the convoluted tubules contained a small amount of granular light yellow pigment.

Study of the liver revealed a marked generalized atrophy of the hepatic cells with a small amount of fatty change. *A single localized lesion* having epithelioid cells, giant cells, and a small amount of caseation necrosis was found. This resembled a miliary tubercle but acid fast stains did not reveal organisms. Silver stains by the method of Levaditi were negative for treponemata. Some of the liver triads showed a moderate increase in fibrous tissue with a marked round cell infiltration. Very small areas of fine fibrous tissue which penetrated to some extent among the surrounding hepatic cells were scattered throughout all liver sections studied. The polygonal cells immediately adjoining these areas were small, shrunken, and occasionally fragmented. Several areas consisting largely of plasma cells and lymphocytes were located in the subcapsular areas. No endarteritis could be demonstrated. The reticulo-endothelial cells of Kupffer were increased in number, and possibly responsible for the hepatomegaly since the polygonal cells appeared small and atrophic. The generalized atrophy of the hepatic cells could be secondary to the long standing anoxemia accompanying the anemic state rather than to a specific disease process. The areas of fibrous tissue, the chronic inflammatory cells, and the small granulomatous area were considered to be evidence of a chronic infection. Sections of both adrenals were normal.

DISCUSSION

Auto-agglutination. The agglutination observed in this case was not that of pseudo-agglutination of the type observed in the hyperglobulinemia sometimes accompanying multiple myeloma, because these agglutinins were absorbed when the clot containing the red cells was left in the serum for six to 12 hours, or when the red cells of a citrated suspension of whole blood were allowed to remain in the plasma from four to eight hours. These agglutinins were not stronger at body temperatures, but on the contrary, slightly weaker; they resisted considerable dilution as demonstrated by the clumping occurring in the red cell counting pipette after undergoing a dilution of 200 times, and gave no indication of specificity in determining blood groups or subgroups. The auto-agglutination first observed by Reimann [3] in multiple myeloma and later by Bonniger [5] and Magnus-Levy [7] was apparently pseudo-agglutination which gave a rouleaux formation that could be broken up by agitation and was not accompanied by subsequent destruction and disintegration of the erythrocytes.

These atypical agglutinins resemble iso-agglutinins in their capacity for absorption, are little affected by temperature changes and stand considerable dilution, but are unlike iso-agglutinins in that no specific blood group is indicated and the patient's own serum acts strongly on the patient's own cells to bring about agglutination and fragmentation and a subsequent slow hemolysis.

These agglutinins conform more nearly to those classified as auto-agglutinins since they are absorbed, tolerate considerable dilution, and indicate no specific blood group or subgroup. Cold agglutinins are active at low temperature and belong to the group of auto-agglutinins. Stewart and Harvey [20] reported a case of hereditary auto-agglutination in which the cold agglutinins were demonstrated in mother and daughter. Wiener [21] considers the presence of non-specific auto-agglutinins as "a normal physiological phenomenon which is present in many animal sera with the titer being greatly increased in certain pathological conditions." This is said by some workers in hematology and immunology to be the basis of the hemolysis occurring in the Donath-Landsteiner test for paroxysmal cold hemoglobinuria, a condition most often associated with syphilis and usually responding to antisyphilitic therapy. McCombs [22] and Boxwell [28] in separate studies, reviewed the cases reported in the literature having auto-hemagglutination. Many of them are clear cut instances of cold auto-agglutination. Other conditions cited as having high titers of auto-agglutinins are syphilitic cirrhosis of the liver, hemolytic icterus, Raynaud's vascular disease, trypanosomiasis, unexplained severe anemias, and obscure instances of no demonstrable disease.

Hyperglobulinemia. Protein values are rarely determined except in conditions of edema when hypoproteinemia is suspected. Hyperproteinemia has been observed mainly in chronic infections such as lymphopathia venereum, granuloma inguinale, chronic tuberculosis, leprosy, sarcoid of Boeck, syphilis, trypanosomiasis, filariasis, occasionally in rheumatoid arthritis, malaria, and in the neoplastic conditions of multiple myeloma, leukemia, lymphosarcoma, and malignant kidney tumors.

In this case protein determinations were carried out because of (1) the clumping of the erythrocytes in the red cell pipettes and sedimentation tubes; (2) the difficulty encountered in cross matching for transfusions; and (3) the serological reactions. Total serum and plasma protein determinations revealed

values of from 9 to 10 grams per 100 c.c., the total increase being caused mainly by elevation of the globulin protein to 5–6 grams per 100 c.c., and an accompanying reversal in the albumin-globulin ratio (chart 2). Except for very rare instances hyperproteinemia is caused by an increase in the globulin fraction above the normal limits of 2.5 to 3.0 grams per cent, thereby causing a reversal of the albumin-globulin ratio, since the albumin content remains normal.

The association of agglutinins with the plasma protein, particularly with one of the globulin fractions, has been indicated by many workers in immunology. Therefore, some type of chronic infection was suspected and searched for in this case, mainly on the basis of increased titer of non-specific auto-agglutinins which may have become elevated along with the production of specific antibodies during the development of immunity to the infection. This could be similar to the cold hemolysins found in rare instances of congenital syphilis, which produce the clinical syndrome of paroxysmal cold hemoglobinuria and give the Donath-Landsteiner phenomenon.

Bing and Plum [24] described an increase in plasma cells and reticulo-endothelial cells in and outside the bone marrow as the consistent pathological feature of hyperglobulinemia. Hyperglobulinemia is not a consistent feature of splenomegaly, even though it has often been observed in chronic infections associated with splenomegaly. Tertiary syphilis with splenomegaly and without alterations in the serum proteins have been observed by the writers. No significant protein changes followed splenectomy in this patient. The site of globulin formation has not been definitely established. Whether it be in the bone marrow, liver, or spleen, apparently the ubiquitous reticulo-endothelial system, if it is concerned with globulin formation, is capable of producing increased globulin levels in conjunction with the production of specific antibodies.

Positive Serological Studies. The behavior of the serologic reactions to various syphilitic antigens is sufficiently atypical to suggest the possibility of false positive reactions. However, inadequate courses of therapy with potassium iodide and bismuth could account for the doubtful to weakly positive serological reactions before splenectomy. The negative serological reactions following splenectomy are difficult to interpret unless this supports the contention that the reticulo-endothelium of the spleen plays a prominent rôle in the production of antibodies.

Use of Gum Acacia. The intravenous administration of gum acacia solution was a last desperate therapeutic effort as all others had been exhausted without success. This was done on the basis of the work of Yuile and Knutti [25] who, by the intravenous use of gum acacia in dogs, reduced the level of blood proteins, the globulin and fibrinogen portions being affected to a greater extent than was the albumin. The procedure was considered safe since the animals used by these workers remained in a satisfactory clinical condition, and acacia has been given on numerous occasions without untoward effects in instances of severe shock from hemorrhage. One injection of 10 grams as a 6 per cent solution in normal saline was given, with a decrease in the total blood protein to 7.75 grams. A greater decrease occurred in globulin than albumin with a subsequent lowering of the reversed albumin-globulin ratio (chart 2). Additional quantities of acacia were not given even though the globulin level had been lowered, mainly because it produced no abatement of the hemolytic crisis.

Diagnostic Possibilities. The clinical features in conjunction with the limited autopsy findings do not permit a clear unequivocal diagnosis. The most likely possibilities would include atypical chronic hemolytic anemia with auto-agglutination and hemolysis secondary to a chronic infection. The exact status of syphilis as the etiological agent cannot definitely be determined. The mother is said to have always been in good health, never had antisyphilitic treatment, no miscarriages, and to have had three normal boys by her second husband. However, the patient and her twin sister had positive serological reactions with various types of syphilitic antigens. The sister had always been well and the patient failed to respond to numerous courses of anti-syphilitic treatment during her five year period of illness. There is a possibility of an acquired syphilis in the patient as well as in her twin sister but from the history this appears unlikely. An enlarged liver with apparent.atrophy of the individual cells, a granulomatous area of almost macroscopic size, and a slight degree of fine fibrosis in scattered areas seem to indicate a chronic infection, whether it be caused by an obscure unrecognized agent or an atypical reaction to syphilis.

An atypical type of familial hemolytic icterus should be considered. Little was known about the paternal side of the family except that the father was a native of Greece. The granulomatous areas present in the liver at autopsy were not typical of familial hemolytic icterus, nor was the fragility test positive. Furthermore, splenectomy did not effect a cure.

Mediterranean anemia in an adult with repeated erythroblastic crises is quite rare. The Grecian ancestry supports this possibility, but this is unlikely in view of the patient's age, lack of bone rarefaction in roentgenographic studies, and the autopsy findings.

No doubt one could apply the label of "acquired hemolytic anemia" to such a syndrome as seen in this patient, but this unsatisfactory designation is hardly adequate for scientific purposes. Moreover patients with the above disease do not show the auto-agglutination and hyperglobulinemia.

CONCLUSIONS

1. There is reported a case of atypical hemolytic anemia with auto-agglutinins and hemolysins associated with or caused by hyperglobulinemia.

2. No syndrome of hemolytic anemia with strong auto-agglutinins and hemolysins accompanied by hyperglobulinemia could be found in the medical literature.

3. Positive serological tests for syphilis, a microscopic granulomatous area in a liver section taken at autopsy along with generalized atrophy of the hepatic cords, and some irregular areas of fibrous tissue with round cell infiltration are presented as strongly indicative of a chronic infection, possibly syphilis.

4. The possible association of hyperglobulinemia with an increased titer of normal non-specific auto-agglutinins as the result of chronic.infection, perhaps an atypical manifestation of syphilis, is discussed.

BIBLIOGRAPHY

1. LANDSTEINER, K.: Ueber Beziehungen zwischen dem Blutserum und den Körperzellen, München. med. Wchnschr., 1903, xlix, 1812. Newer knowledge of immunology and bacteriology, 1928, University of Chicago Press, Chicago, 898.

2. LEVINE: Ukrain. Zentralbl. f. Blutgruppen-forsch., 1928, ii, 1.

3. REIMANN, R. A.: Hyperproteinemia as a cause of autoagglutination; observations in a case of myeloma, Jr. Am. Med. Assoc., 1932, xcix, 1411.

4. JACOBSON, B. M.: On a peculiar serum protein, precipitated by Hayem's solution, occurring in multiple myeloma, Proc. Soc. Exper. Biol. and Med., 1935, xxxii, 1257.

5. BONNIGER, M.: Ein seltener Blutefund (Hyproteinamis bei Myelomkrankheit), Deutsch. med. Wchnschr., 1933, lix, 770–771.

6. SWEIGERT, C. F.: Multiple myeloma with hyperproteinemia; case report, Am. Jr. Med. Sci., 1935, cxc, 245.

7. MAGNUS-LEVY, A.: Multiple myelome. VII. Euglobulinemia. Zur Klink und Pathologie der Amyloidosis, Ztschr. f. klin. Med., 1933, cxxvi, lxii, 62–111.

8. ANTOPOL, W., APPLEBAUM, I., and GOLDMAN, L.: Two cases of acute hemolytic anemia with autoagglutination following sulfanilamide therapy, Jr. Am. Med. Assoc., 1939, cxiii, 488.

9. WU, H.: A new colorimetric method for the determination of plasma proteins, Jr. Biol. Chem., 1922, li, 33.

10. LUTHY, F.: Klinische Untersuchungen über Serumeiweiskörper bei Lungentuberculose, Schweiz. med. Wchnschr., 1927, lvii, 993.

11. LEDENTU, G., and VAUCEL, M.: La formol gelification dans la trypanosomiase humaine, Bull. Soc. path. exot., 1927, xx, 601.

12. CHOPRA, R. N., MUKHERJEE, S. N., and RAO, S. S.: Studies on protein fractions of blood sera; normal and filarial blood sera, Indian. Jr. Med. Research, 1934, xxii, 171.

13. MELENEY, H. E., and WU, H.: Blood serum globulin in schistosomiasis japonica, China Med. Jr., 1924, xxxviii, 357.

14. SALVESEN, H. A.: The sarcoid of Boeck, a disease of importance to internal medicine, Acta Med. Scandin., 1935, lxxxvi, 127.

15. GUTMAN, A. B., and GUTMAN, E. B.: Calcium-protein relation in hyperproteinemia: Total and diffusible serum calcium in lymphogranuloma inguinale and myeloma, Proc. Soc. Exper. Biol. and Med., 1936, xxxv, 511.

16. SIA, R. H. P., and WU, H.: Serum globulin in Kala-azar, China Med. Jr., 1921, xxxv, 527.

17. LOEPER, M., FORESTIER, J., and TONNET, J.: L'hyperalbuminose paradoxale du sang des cancereux, Presse méd., 1921, xxix, 333.

18. GUTMAN, A. B., GUTMAN, E. B., JILLSON, R., and WILLIAMS, R. D.: Acid-base equivalance of blood in diseases associated with hyperglobulinemia; with especial reference to lymphogranuloma inguinale and multiple myeloma, Jr. Clin. Invest., 1936, xv, 475.

19. JEGHERS, H., and SELESNICK, S.: Hyperproteinemia: its significance, Internat. Clin., 1937, iii, 248–279.

20. STEWART, W., and HARVEY, E. E.: Blood transfusion in two cases of autoagglutination, Lancet, 1931, ii, 399.

21. WIENER, A. S.: Blood groups and blood transfusion, 2nd edit., 1939, Chas. C. Thomas, Springfield, Illinois.

22. McCOMBS, R. P., and McELROY, J. S.: Reversible autohemagglutination with peripheral vascular symptoms, Arch. Int. Med., 1937, lix, 107.

23. BOXWELL, W., and BIGGER, J. W.: Autohemagglutination, Jr. Path. and Bact., 1931, xxxiv, 407.

24. BING, J., and PLUM, P.: Serum proteins in leucopenia (contribution on question about place (for formation of serum proteins), Acta med. Scandin., 1937, xcii, 415.
    BING, J.: Further investigations on hyperglobulinemia (is serum-globulin formed from plasma cells and reticulo-endothelial cells?), Acta med. Scandin., 1940, ciii, 565.

25. YUILE, C. L., and KNUTTI, R. E.: Blood plasma protein as influenced by intravenous injection of gum acacia. The production of chronic hypoproteinemia, Jr. Exper. Med., 1939, lxx, 605.

THE CONTROL OF MASSIVE PULMONARY HEMORRHAGE BY PNEUMOPERITONEUM *

By Arthur J. Logie, M.D., F.A.C.P., Harrison A. Walker, M.D., F.A.C.S., and Guy R. Stoddard, M.D., *Miami Beach, Florida*

Artificial pneumoperitoneum has become a valuable addition to the armamentarium of the phthisiologist in the treatment of selected cases of pulmonary tuberculosis.[1] The safety of inducing and maintaining a pneumoperitoneum, particularly from the pathological aspect, appears well established. Reports of repeated studies on autopsy material stress the fact that there are no changes in the abdominal viscera which can be attributed to the air introduced into the peritoneal space.[2]

Although uncontrollable hemorrhage from the lungs is considered an indication for this type of therapy, there is no mention in the literature of a case treated in this manner. It is apparent, however, that pneumoperitoneum has been successfully employed to control repeated small hemoptyses. The following is a case in which pneumoperitoneum was used for massive pulmonary hemorrhage, and in which the procedure proved dramatically effective.

Case Report .

J. W., a white male, aged 25 years, was admitted to the St. Francis Hospital with a history of having coughed up about one teacupful of bright red blood the previous day. He had contracted an upper respiratory infection one week prior to admission and had expectorated blood-tinged sputum frequently. . A history of recurrent pneumonias and several attacks of pleurisy affecting the left side of the chest was obtained. The first pneumonia occurred in 1936 and involved both lungs. Subsequently, the patient developed a persistent, productive cough. His condition was studied at the Chevalier Jackson Clinic in Philadelphia where numerous bronchoscopies were done, and a diagnosis of bronchiectasis affecting the bases of both lungs was reached.

In the early part of 1939, the patient suffered a second attack of pneumonia which involved the left lung and was accompanied by a marked pleuritis. In the spring of that year, he was hospitalized for one week because of repeated hemoptyses. Upon recovery, he was advised to reside in a more equable climate, such as that found in Florida.

Except for the diseases common to childhood, the patient had been free of any major illness until 1936. Although he had developed chest colds frequently, he denied having any symptoms of sinus trouble. There was no history of familial cancer, lung disease, or any known contact with tuberculosis. The patient's wife was receiving treatment for a severe Vincent's angina at the time his present illness began, but there was no evidence that the spirochetal infection had been transmitted to or from the patient.

On August 29, 1941, the day of admission to the hospital for his present condition, the patient appeared pale, weak, apprehensive, and acutely ill with temperature of 99° F., pulse 104, respiration 24, and blood pressure of 118 mm. Hg systolic and 74 mm. diastolic. He had a frequent, harsh cough and expectorated a scant amount of blood-streaked sputum. Physical examination revealed the following positive findings: pale conjunctivae and fundi, granular and inflamed pharyngeal mucous membranes, slight postnasal drip, moderate-sized blood clot in the posterior nasopharynx, cold, moist

skin of poor texture, and cyanotic fingernail beds. His chest was symmetrical in size and shape, and expanded evenly and equally in its upper part but lagged at the left base during respiration. There was a hyper-resonant note on percussion over the base of the right lung and dullness at the left base. Many sonorous and sibilant râles were heard over the right base, anteriorly and posteriorly, and to a lesser degree at the left base, where the breath sounds were diminished in intensity. Laboratory

FIG. 1. Roentgenogram of chest before treatment.

study showed the following: red blood cells 4.5, hemoglobin 13.68 grams (86 per cent), white blood cells 16,000, polymorphonuclears 50 per cent, segmented 41 per cent, nonsegmented 9 per cent, and lymphocytes 50 per cent; clotting time 2 min. 50 sec., and bleeding time 45 sec.

Treatment was directed primarily toward preventing further hemorrhage and replacing the blood loss. Oxygen was given for the anoxemia, and sedatives for the cough, restlessness, and apprehension. August 30, 1941, the patient suddenly coughed up approximately 675 c.c. fresh blood. Two days later, September 1, 1941, he was

awakened by a spasm of coughing and expectorated 200 c.c. blood. That afternoon he had another hemorrhage of 200 c.c. In the evening his temperature rose to 102.6° F., pulse 125, and respiration 36. The laboratory examinations showed: red blood cells 3.6, hemoglobin 10.62 grams (67 per cent), white blood cells 22,300, polymorphonuclears 80 per cent, segmented 56 per cent, nonsegmented 21 per cent, juveniles 3 per cent, and lymphocytes 20. Roentgenograms of his chest showed a diffuse, mottled shadow in the right lower lobe, close to the cardiac border, which was suggestive of an acute pneumonitis, and also changes caused by the aspiration of blood. A dense shadow, triangular in outline, extended from the left hilum area downward and laterally into the left base, and appeared to be an atelectatic left lower lobe. The trachea was slightly displaced toward the left side (figure 1).

Although there was a difference of opinion regarding the site of the hemorrhages, it was considered probable that the bleeding originated in the left lung. However, in view of the history of recurrent pleurisy on the left side, the possibility of obtaining a satisfactory collapse of the bleeding area in that lung by artificial pneumothorax seemed very unlikely. Bronchoscopy was considered inadvisable at this time because of the patient's grave condition and the recent bleeding. Sulfathiazole, coagulants, and a transfusion of 300 c.c. citrated blood were administered. The following day, September 2, 1941, the patient was given another transfusion of 300 c.c. citrated blood, and also 10 per cent dextrose in Ringer's solution. On September 3, 1941, the patient experienced a marked reaction to a transfusion of 400 c.c. citrated blood in the form of a severe chill and a sharp rise of temperature to 106° F. The therapy now included calcium, parathyroid extract, vitamins C, D, and K, and thromboplastin. The sulfathiazole concentration in the blood had now reached 6 mg. per cent.

On September 4, 1941, he had two hemorrhages of 150 c.c., and 90 c.c. respectively. Blood culture was negative for organisms; the red blood cell count fell to 3.5, the hemoglobin to 10 grams (63 per cent). Sputum smear and culture were negative for acid-fast bacilli, but showed many Gram-negative cocci and bacilli, *N. catarrhalis*, and *Staphylococcus albus*. No spirochetes were reported. The patient was placed within an oxygen tent and frequent but small amounts of whole blood were given daily by direct transfusion. Citrated blood was replaced by whole blood as the former seemed to increase the patient's tendency to hemorrhage. However, on September 7, 1941, another hemorrhage of 90 c.c. blood occurred. A roentgenogram of the chest revealed some clearing of the mottled shadow at the base of the right lung, and increased aeration of the atelectatic left lower lobe.

During the next day, the patient experienced three hemorrhages, 1500 c.c., 150 c.c., and 90 c.c., respectively. As mechanical compression of the bleeding area appeared to be the only practicable method of preventing further hemorrhage, artificial pneumoperitoneum was induced. The patient, being too dyspneic to lie flat upon his back, was placed in the Fowler position for this procedure. His bladder was emptied, and 1000 c.c. air were injected intraabdominally at a point two fingers' breadth above and to the left of the umbilicus. The intraperitoneal pressure was raised to plus 7 mm. water. A roentgenogram of the chest showed a one inch separation of the diaphragm from the abdominal organs, but there was no apparent elevation of the diaphragm as regards rib level. The patient's temperature had risen to 102° F., the red blood cells had fallen to 3.2, the hemoglobin to 9.37 grams (59 per cent), and the color index to 0.92. The white cell count was 13,800, polymorphonuclears 59 per cent, segmented 45 per cent, nonsegmented 13 per cent, juveniles 1 per cent, and lymphocytes 41 per cent.

For several days there was slight fever with an evening rise to 100° F. After freedom from bleeding for seven days, the patient, on September 16, 1941, had three hemorrhages of 25 c.c., 75 c.c., and 25 c.c. fresh blood. That day, a pneumoperitoneum refill was given—1000 c.c. air with a final pressure of plus 8 mm. water. The

following day, the patient coughed up about 10 c.c. bright red blood. On September 18, 1941, a 300 c.c. hemorrhage occurred.

At this time it was decided that pneumoperitoneum refills would be given every second day in order to obtain a maximum elevation of the diaphragm. At each refill the amount of air administered would be increased until the intraperitoneal pressure reached the highest point that the patient could tolerate without too much discomfort.
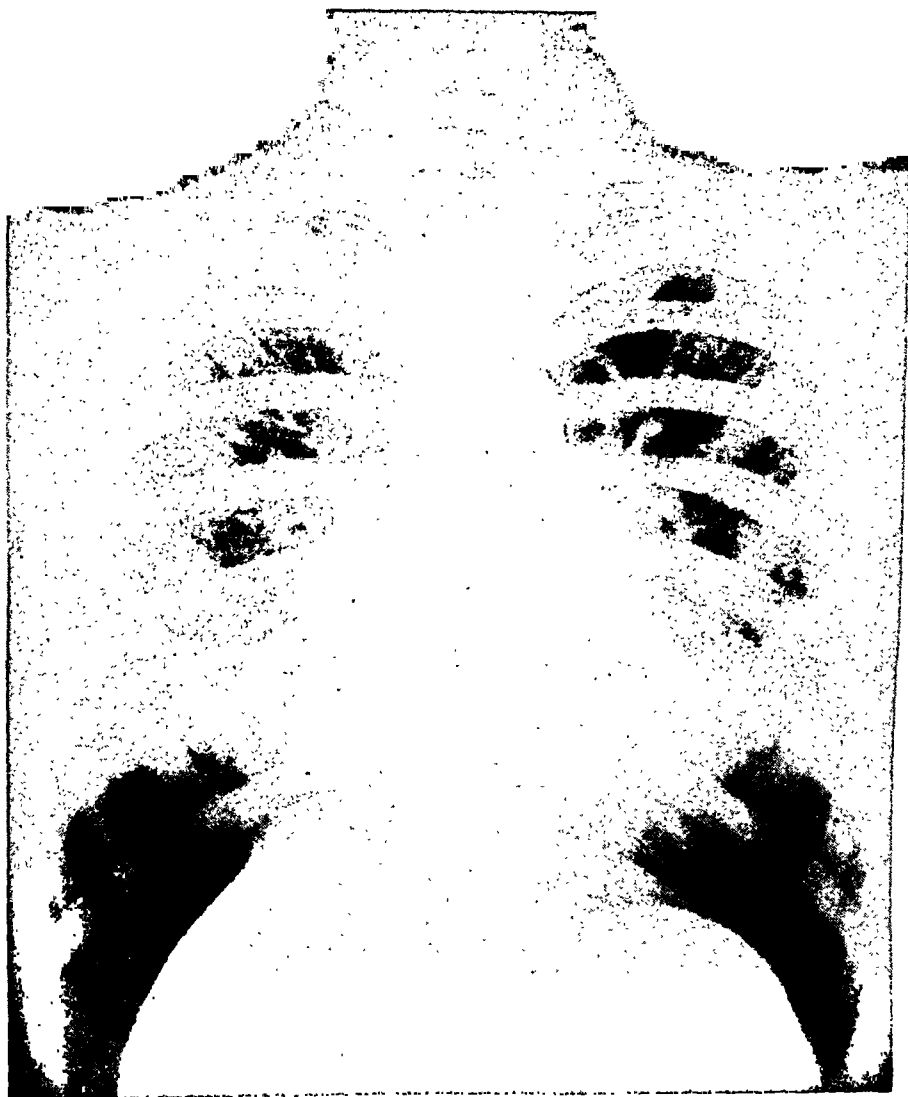
FIG. 2. Roentgenogram of chest after pneumoperitoneum was established.

It was also agreed that a temporary phrenic nerve crush would be performed to supplement the action of the pneumoperitoneum, if the pneumoperitoneum, itself, failed to control the bleeding.

Despite this régime, the patient bled twice on September 21, 1941, losing 1100 c.c. and 150 c.c. blood. Another hemorrhage of 850 c.c. took place on September 24, 1941. It was evident that the air introduced into the peritoneal cavity was being absorbed very rapidly. Amounts of air had been administered every other day to raise the intraperitoneal pressure to plus 14 mm.–16 mm. water. Nevertheless, at each refill

FIG. 3. Chart summarizing data as to hemorrhages and results of treatment.

the initial manometer reading was found to be less than plus 7 mm. water. Consequently, it was necessary to institute a course of daily pneumoperitoneum refills. Each day approximately 1000 c.c. air were injected to maintain the intraperitoneal pressure at plus 16 mm. to plus 18 mm. water.

As the patient's sputum had been free of blood for three days, and as there was considerable discomfort due to the marked abdominal distention, which was not relieved by changes in position, the refill for September 27, 1941 was omitted. That night he awoke and coughed up frothy mucopurulent sputum containing about 250 c.c. fresh blood. Daily pneumoperitoneum refills were resumed and continued for the next seven days. There were no further hemorrhages, and the sputum became clear of any trace of blood within a few days. The patient began to expectorate foul-smelling material copiously. At this stage, a chest roentgenogram showed further clearing at the base of the right lung, and increased aeration of the left lower lobe. The diaphragm was elevated to the level of the eighth rib on the right side and to the eighth intercostal space on the left (figure 2). This was an appreciable rise as compared to previous films of the chest taken at the same phase of respiration.

Beginning on October 4, 1941, 100 c.c. to 300 c.c. air were aspirated from the peritoneum at intervals, reducing the intraperitoneal pressure to plus 4 mm. water. The air remaining in the peritoneal space was left to be absorbed spontaneously.

Subsequently, the patient's recovery was uneventful. He had lost 18 pounds during his acute illness but regained eight pounds prior to his discharge from the hospital. He was allowed out of bed for the first time on October 9, 1941. He was referred to the Chevalier Jackson Clinic on November 2, 1941 for further study in preparation for lobectomy. At the time of discharge his temperature had been normal for one month. Laboratory study showed the following: red blood cells 4.5, hemoglobin 13.68 grams (86 per cent), C. I. 0.95, and white blood cells 5000. His final chest film revealed the diaphragm elevated to the level of the lower border of the ninth rib, complete resolution of the shadow at the base of the right lung, and a well aerated left lower lobe. A partial pneumoperitoneum was still present, and the intraperitoneal pressure was equal to plus 3 mm. water.

In all, 14 pneumoperitoneum refills were administered, making a total of approximately 14,500 c.c. air. Despite daily refills of about 1000 c.c. air, no complications occurred. The only untoward effect of maintaining the exceedingly high intraperitoneal pressure consisted of moderate discomfort due to the marked abdominal distention, which was usually relieved by elevating the foot of the patient's bed. There could be no doubt that the pneumoperitoneum was effective in controlling the pulmonary hemorrhages. From the date of admission, the patient had 19 hemorrhages, 16 of them massive, and had lost over 6000 c.c. blood within the period of less than 30 days. In that period, he received 13 transfusions, making a total of approximately 5000 c.c. blood (figure 3).

BIBLIOGRAPHY

1. BANYAI, A. L.: Therapeutic pneumoperitoneum, Am. Rev. Tuberc., 1934, xxix, 603.
2. FOWLER, W. O.: Pneumoperitoneum in the treatment of pulmonary tuberculosis, Am. Rev. Tuberc., 1941, xlix, 474–478.

EDITORIAL

ANTIBIOTIC SUBSTANCES PRODUCED BY MICROÖRGANISMS

MANY instances are known in which the presence and growth of one microörganism is antagonistic to the growth and multiplication of another species. One of the best examples of this action became known through the observation of Fleming[1] that colonies of a certain species of mould (*Penicillium notatum*) inhibited the growth of colonies of many species of bacteria in their vicinity. He showed that the inhibiting substance, which he named penicillin, was present in broth culture filtrates of the organism. He demonstrated that its action was selective and limited largely to Gram-positive organisms, particularly the pyogenic cocci. On the other hand it had little or no effect on Gram-negative organisms of the typhoid-colon group or on Pfeiffer's influenza bacillus. Isolation of the latter was facilitated by adding penicillin to the culture media in order to inhibit the growth of other organisms.

Fleming also reported that penicillin was nonirritant and nontoxic to animals, even in large doses, and suggested that it might be effective in treating infections due to organisms susceptible to its action. However, no active interest in its clinical use was aroused until Chain, Florey, et al.[2,3] again demonstrated its lack of toxicity for mice and reported its successful use in a small series of human infections.

Another important contribution was made by Dubos[4,5] who, by an ingenious method, isolated from soil a Gram-positive spore-bearing bacillus (later known as *Bacillus brevis*) which exerted a powerful bactericidal effect on many Gram-positive organisms, including pneumococci, hemolytic streptococci and staphylococci. The active substance was present in the culture medium after autolysis of the organisms. Administered intraperitoneally, it protected mice from large doses of virulent pneumococci similarly injected, and exhibited some curative effect. The active substance, to which the name tyrothricin was later given, was found to contain two active ingredients, tyrocidin and gramicidin, both polypeptids. The latter was much the more potent and important. In amounts as small as one microgram per c.c. it prevented growth of pneumococci in broth cultures, and from one to five micrograms, injected intraperitoneally, protected mice

[1] FLEMING, A.: The antibacterial action of cultures of a *Penicillium*, with special reference to their use in the isolation of B. *influenzae*, Brit. Jr. Exper. Path., 1929, x, 226.
[2] CHAIN, E., FLOREY, H. W., et al.: Penicillin as a chemotherapeutic agent, Lancet, 1940, ii, 226–228.
[3] ABRAHAM, E. P., CHAIN, E., et al.: Further observations on penicillin, Lancet, 1941, ii, 177.
[4] DUBOS, R. J.: Studies on a bactericidal agent extracted from a soil bacillus. I. Preparation of the agent. Its activity in vitro, Jr. Exper. Med., 1939, lxx, 1.
[5] DUBOS, R. J.: Studies on a bactericidal agent extracted from a soil bacillus. II. Protective effect of the bactericidal agent against experimental pneumococcus infections in mice, Jr. Exper. Med., 1939, lxx, 11.

from one million fatal doses of culture similarly administered. It was actively hemolytic, and in somewhat larger doses was highly toxic for these animals.

Tyrothricin has had a fairly extensive trial in cases of human infection, and it has been highly effective against pneumococcus and streptococcus infections (but only feebly so in staphylococcus infections) when applied locally to external wounds, ulcers or sinus tracts, to the mucosa of the nasopharynx, the bladder, or the pleura in empyema.[6, 7, 8] It was found to be too toxic for parenteral administration, however, and is ineffective by mouth. When given intravenously to animals with systemic infections it was practically inert. Its usefulness is therefore strictly limited to superficial infections in which it can be brought into direct contact with the microorganisms concerned.

The promising if restricted results obtained clinically by the use of gramicidin and particularly of penicillin [3] naturally stimulated a search for similar substances produced by other organisms, especially among the moulds. A number of such antibiotic principles have been demonstrated. Thus from species of *Actinomyces* three distinct substances have been obtained: actinomycetin (a polypeptid), streptothricin (an organic base), and actinomycin (a pigment). Fungi of the genus *Aspergillus* have contributed several. Among these are aspergillin, from *A. flavus;* fumagacin, from *A. fumagatus,* and clavacin (a lipoid) from *A. clavatus.* Gliotoxin was obtained from *Gliocladium fimbriatum,* and claviformin from *Penicillium claviforme.* Other antibiotics which differ from penicillin chemically and in their range of action have been isolated from cultures of *Penicillium notatum.*

These substances differ considerably from one another in their chemical characteristics, potency, range of action and toxicity. Some are active on bacterial species not affected by penicillin. Most of them are relatively ineffective on Gram-negative bacilli, but streptothricin is an exception in this respect. Most of them are more or less toxic for animals, some highly so. The more important of these antibiotics have been studied and compared by Waksman.[9, 10] None has yet been sufficiently studied to determine its clinical usefulness. There can be little doubt, however, that eventually some such products will be found which will supplement the many deficiencies of penicillin and possibly supplant it entirely.

Following the publications of Florey et al., interest has centered in penicillin, and clinical tests have been carried out as extensively as the scanty quantities available permitted. Their results have been confirmed and ex-

[6] HERRELL, W. E., and HEILMAN, D.: Experimental and clinical studies on gramicidin, Jr. Clin. Invest., 1941, xx, 583.

[7] RAMMELKAMP, C. H.: Use of tyrothricin in the treatment of infections, War Med., 1942, ii, 830.

[8] BORDLEY, J. E., CROWE, S. J., et al.: The local use of the sulfonamides, gramicidin (tyrothricin) and penicillin in otolaryngology, Ann. Otol., Rhin. and Laryng., 1942, li, 936.

[9] WAKSMAN, S. A., and WOODRUFF, H. B.: Selective bacteriostatic and bactericidal action of various substances of microbial origin, Jr. Bact., 1942, xliii, 9.

[10] WAKSMAN, S. A.: Nature and mode of action of antibiotic substances, Jr. Bact., 1943, xlv, 64.

tended by (among others) Herrell and associates, Rammelkamp and Keefer, and Florey and Florey. Finally Keefer and associates [11] have just reported the results of the treatment of 500 cases of various infections, carried out under the auspices of the Committee on Chemotherapeutic and Other Agents, Division of Medical Sciences, National Research Council. This report should be read carefully by everyone interested in the subject.

One of the most valuable properties of penicillin is its almost complete lack of toxicity, even when given intravenously in very large doses. Apparently penicillin will accomplish all or nearly all that can be done by the sulfonamides as well or better than they, with negligible chance of toxic reactions. It is highly effective against pneumococcus, hemolytic streptococcus and gonococcus infections, including those caused by strains which are resistant to sulfonamides. It is much superior to sulfonamides in the case of staphylococcus infections, although relatively large doses are required. Of 91 cases of *Staphylococcus aureus* sepsis, 60 per cent recovered or greatly improved,[11] in contrast with the average mortality in untreated cases of this type of about 85 per cent. There is reason to hope that it will be effective also in infections with the Gram-positive anaerobic bacilli.

In view of the great interest and perhaps rather uncritical enthusiasm which penicillin has aroused, it seems desirable to emphasize its defects and limitations as well as its remarkable therapeutic powers.

One of the most serious obstacles to the use of penicillin is the difficulty of preparing it in quantity and its high cost. Only minimal amounts are produced in the cultures, and it is so unstable that a substantial part is lost during its recovery and purification. Florey [3] in connection with his earlier preparations reported that the crude filtrate contained from one to two units per c.c., and that only one-third of this was recovered, so that 100 liters of culture were required to produce one gram of therapeutic material containing 40 to 50 units per mg. (50,000 units in all). One Oxford unit was defined as the minimum amount of penicillin which would completely inhibit the growth of a test strain of *Staphylococcus aureus* when dissolved in 50 c.c. of meat extract broth. Further purification yielded a product containing about 500 units per mg., but with additional loss in the yield. As the amount recommended for the treatment of a severe infection is about 120,000 units a day, and as administration may have to be continued for 7 to 14 days, it is obvious why the use of penicillin is still on a very restricted experimental basis and why it is still unobtainable for general civilian use.

The intensive efforts being made to improve the methods of production have doubtless increased the yield substantially, but Richards [12] has recently stated that one gram from 20 liters of culture would be exceptionally high. Merely to supply the expected needs of the armed forces is a herculean task which seems practically an impossibility unless a method of synthesizing

[11] KEEFER, C. S., BLAKE, F. G., MARSHALL, E. K., JR., LOCKWOOD, J. S., and WOOD, W. B.: Penicillin in the treatment of infections; Statement by the Committee on Chemotherapeutic and Other Agents, Division of Medical Sciences, National Research Council, Jr. Am. Med. Assoc., 1943, cxxii, 1217.

[12] RICHARDS, A. N.: Penicillin. Statement released by the Committee on Medical Research, Jr. Am. Med. Assoc., 1943, cxxii, 235.

penicillin can be devised. Reports so far published give very little information as to its structure, but its apparent relative complexity and marked instability suggest that synthesis may prove a tedious and difficult task.

The administration of penicillin also offers some practical difficulties. The action of penicillin is largely bacteriostatic, only in part bactericidal, particularly on staphylococci. To be effective, the organisms must be kept continuously in contact with penicillin in adequate concentration (about 0.02 to 0.15 units per c.c.[13]) until recovery is complete. Penicillin is inert by mouth, and must be given by parenteral injection. When so given it is so rapidly excreted in the urine that, in order to maintain an effective concentration in the blood, it must be given by continuous intravenous drip or by intravenous or intramuscular injections repeated every two to four hours. Hobby et al. have reported that mice can be protected from pneumococcal and streptococcal infection by a single subcutaneous injection of an oil suspension of penicillin, and by the subcutaneous implantation of a single pellet mixed with cholesterol. It seems possible that some similar procedure might be devised for the treatment of human cases.

It is probable that penicillin will be effective in the treatment of meningococcus infections, as it acts strongly on this organism in vitro. As little if any penicillin enters the spinal fluid after intravenous injection, it is probable that intrathecal as well as intravenous injections will be required in cases of meningitis.

Penicillin-fast strains have been reported in the case of pneumococci, hemolytic streptococci and staphylococci. This resistance may develop either in vivo or in vitro, but it appeared only after protracted continuous exposure of the organisms to penicillin. Such strains, however, were found to have largely lost their virulence, and they continued to be sensitive to the sulfonamides.

Penicillin is definitely restricted in the range of its activities, and there are many organisms that are resistant. As far as present studies go, there is a close parallelism between its activities in vitro and in vivo. It has no action on *Streptococcus fecalis* and on some other strains of *Streptococcus viridans*. It had no effect, or only a very temporary one in 17 cases of subacute bacterial endocarditis in which it was tried. Like the sulfonamides, it seemed to cause temporary sterilization of the blood stream in a few cases.

Penicillin has been reported to be inactive in vitro and in some cases in vivo toward the Gram-negative bacilli of the colon, typhoid, *Salmonella* and dysentery groups, toward *Brucella,* the influenza bacillus, Friedländer's bacillus, *Proteus,* the pyocyaneus bacillus, the cholera vibrio and the tubercle bacillus.

In spite of these drawbacks, penicillin is a remedy of extraordinary value. The perfection of some method which would make possible its production on a large scale and at reasonable cost would be a therapeutic advance comparable in importance to the discovery of the sulfonamides.

[13] RAMMELKAMP, C. H., and KEEFER, C. S.: Penicillin; its antibacterial effect in whole blood and serum for the hemolytic streptococcus and *Staphylococcus aureus,* Jr. Clin. Invest., 1943, xxii, 649.

REVIEWS

The Addendum to the Chemistry of the Amino Acids and Proteins. Edited by CARL L. A. SCHMIDT, M.S., Ph.D., Professor of Biochemistry and Dean of the College of Pharmacy, University of California. 12 contributors. 1290 pages; 17 × 26 cm. Charles C. Thomas, Springfield, Ill. 1943. Price, $5.00.

This book, designed to bring the chemistry of the amino acids and proteins up to date in lieu of a completely revised second edition, serves its purpose very well. The added material, covering the period from 1937 to 1942, is arranged in chapters which follow the numbering of the parent volume for easy reference. There is a good bibliography. The addendum also appears as a supplement to the second edition of "The Chemistry of the Amino Acids and Proteins."

<div align="right">M. A. A.</div>

BOOKS RECEIVED

Books received during August are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Hypertension. By IRVINE H. PAGE, A.B., M.D. 80 pages; 19.5 × 13 cm. 1943. Charles C. Thomas, Springfield, Illinois. Price, $1.50.

Handbook of Tropical Medicine. By ALFRED C. REED, M.D., and J. C. GEIGER, M.D. 188 pages; 17 × 11.5 cm. 1943. Stanford University Press, Stanford University, California. Price, $1.50.

Notes on Gas Gangrene. Prevention—Diagnosis—Treatment. By the War Wounds Committee of the Medical Research Council and the Committee of London Sector Pathologists. 28 pages; 24.5 × 15.5 cm. 1943. His Majesty's Stationery Office, London. Price, 6d. net. (Medical Research Council War Memorandum No. 2—Revised Second Edition.)

Kaiser Wakes the Doctors. By PAUL DE KRUIF. 158 pages; 21 × 14 cm. 1943. Harcourt, Brace and Company, 383 Madison Avenue, New York City. Price, $2.00.

COLLEGE NEWS NOTES

ADDITIONAL A. C. P. MEMBERS IN THE ARMED FORCES

Already published in preceding issues of this journal were the names of 1,471 Fellows and Associates of the College on active military duty. Herewith are reported the names of 11 additional members, bringing the grand total to 1,482.

Samuel C. Arnett, Jr.
Roland W. Banks
Meyer Bloom
Mahlon H. Delp
George C. Griffith
Henry B. Gwynn

Tim J. Manson
Henry C. Rosenstiel
Lauren H. Smith
Albert M. Snell
Charles E. Thompson

NEW LIFE MEMBER OF THE COLLEGE

Dr. John Robert Van Atta, F.A.C.P., Albuquerque, N. M., has subscribed to Life Membership, and his initiation fee and Life Membership subscription have been added to the permanent Endowment Fund of the College.

GIFTS TO THE COLLEGE LIBRARY

We gratefully acknowledge receipt of the following gifts to the College Library of Publications by Members:

Books

Dr. Maxwell Finland, F.A.C.P., Boston, Mass.—2 bound volumes, "Collected Reprints";
Dr. James H. Hutton, F. A. C. P., Chicago, Ill.—"War Endocrinology."

Reprints

Dr. John D. Adcock (Associate), Ann Arbor, Mich.—4 reprints;
Dr. Otis L. Anderson, F.A.C.P., U. S. Public Health Service, Bethesda Station, Md. —4 reprints;
Dr. George E. Baker, F.A.C.P., Casper, Wyo.—2 reprints;
J. Edward Berk, F.A.C.P., Captain, (MRC), U. S. Army—1 reprint;
Dr. Verne S. Caviness, F.A.C.P., Raleigh, N. C.—2 reprints;
Edgar Durbin, F.A.C.P., Lieutenant Colonel, (MRC), U. S. Army—1 reprint;
Dr. Hyman I. Goldstein (Associate), Camden, N. J.—1 reprint;
Jack D. Kirshbaum (Associate), Major, (MRC), U. S. Army—3 reprints;
Alfred L. Kruger (Associate), Captain, (MRC), U. S. Army—7 reprints;
Dr. Jerome A. Marks, F.A.C.P., New York, N. Y.—1 reprint;
Benjamin H. Neiman (Associate), Major, (MRC), U. S. Army—1 reprint;
Dr. Aaron E. Parsonnet, F.A.C.P., Newark, N. J.—1 reprint;
Dr. Marjorie E. Reed, F.A.C.P., Plymouth, Pa.—1 reprint;
Eugen G. Reinartz, F.A.C.P., Brigadier General, (MC), U. S. Army—3 reprints;
Howard A. Rusk, F.A.C.P., Major, (MRC), U. S. Army—2 reprints;
Dr. Howard Wakefield, F.A.C.P., Chicago, Ill.—1 reprint;
Dr. Albert Weinstein, F.A.C.P., Nashville, Tenn.—1 reprint.

COLLEGE COMMITTEES AND REGENTS TO MEET, NOVEMBER 19–20

The regular autumn meeting of the College Committees and of the Board of

Regents will be held at the College Headquarters, Philadelphia, Friday and Saturday, November 19-20, to transact the customary business of the College and to pass upon the credentials of candidates for Associateship and Fellowship. Proposals of candidates must be filed in the Executive Offices of the College thirty days in advance of action. The next succeeding meeting will be held in the late winter.

A. C. P. Postgraduate Course and Regional Meeting, Philadelphia

Postgraduate Course No. 3, "Special Medicine," in the series of courses offered by the College to its members during the autumn of 1943, will be held in various Philadelphia institutions during the two-week period, November 8-19. The program is unique in that it allots approximately one-half day to the consideration of each of several special fields of medicine and will be given in eleven different institutions in Philadelphia. The faculty consists of one hundred and three teachers, all recognized authorities in their special fields.

The concluding day, Friday, November 19, will be devoted to a Regional Meeting of the College for Pennsylvania, New Jersey, Delaware, and adjacent territory. The Regional Meeting program will consist of a morning program of clinical presentations at the Hospital of the University of Pennsylvania and of an afternoon scientific program of six papers by eminent authorities, Service and Civilian. In the evening there will be a cocktail party and dinner meeting at which will be represented in person or by envoy, the Surgeons General of the U. S. Army and U. S. Navy, and other distinguished medical men. Timely, short addresses will be given by the President of the College and others.

Dr. Ward Darley, F.A.C.P., Denver, Colo., has retired from private practice in order to accept a full-time teaching post as Associate Professor of Medicine at the University of Colorado School of Medicine.

Dr. Franklin H. Top (Associate), Director of the Division of Communicable Diseases and Epidemiology of the Detroit (Mich.) Department of Health, has been appointed also Medical Director of the Herman Kiefer Hospital, Detroit.

New Acting Governor for Maine

Owing to active military service in the U. S. Navy, Lieutenant Commander Eugene H. Drake, College Governor for Maine, has been granted leave of absence and Dr. Richard S. Hawkes of Portland, Maine, has been named the Acting Governor by the Executive Committee of the Board of Regents.

Dr. Carleton B. Peirce, F.A.C.P., Montreal, Can., has been appointed by the Governors of McGill University as Chairman of the Department of Radiology in the Faculty of Medicine as of June 1, 1943. Dr. Peirce for the past year has been on loan from the Royal Victoria Hospital and McGill University to the Royal Canadian Navy as the Consultant Radiologist for that Service, but at the same time he has been devoting as much time as possible to his responsibilities as Radiologist-in-Chief at the Hospital and to his teaching work at McGill University.

Dr. Carroll M. Pounders, F.A.C.P., Oklahoma City, Okla., has been appointed by the President of the Southern Medical Association as the Oklahoma representative on its Council.

Dr. Christopher G. Parnall, F.A.C.P., Medical Director of the Rochester (N. Y.) General Hospital, has been granted a leave of absence to serve as Director of a survey of twenty-six state operated mental hospitals, the survey being provided for under the Moreland Act. There will be six main divisions of study: "Studies and inquiries into admission and discharge procedures, personnel, professional care of patients, physical plans in the hospital structures, collection of funds for patient care, and administration." Dr. Parnall will be assisted by a staff of experts.

AMERICAN BOARD OF PEDIATRICS EXAMINATIONS

The American Board of Pediatrics has announced its written examination locally under a monitor, February 4, 1944. Its oral examinations will be held in Philadelphia, March 25–26, and in San Francisco, May 6–7. C. A. Aldrich, M. D., Secretary, 707 Fullerton Ave., Chicago, Ill.

At the recent annual meeting of the Chicago Society of Internal Medicine, the following officers were elected for 1943–44: President, Dr. Italo F. Volini, F.A.C.P.; Vice-President, Dr. Howard Wakefield, F.A.C.P.; Secretary, Dr. Howard L. Alt.

Baylor University College of Medicine has moved its equipment from Dallas to Houston where it has set up temporary quarters for the future conduct of the School. The Jefferson Davis Hospital and the Hermann Hospital furnish clinical accommodations. Houston physicians are coöperating in the teaching. Eighty-four students are in the freshman class, but the upper classes are smaller. The School, while still in Dallas, had Army and Navy contracts, and it is said that all the Navy students who were in Dallas have been ordered to Houston. Dr. James A. Greene, F.A.C.P., formerly Associate Professor of Medicine at the State University of Iowa College of Medicine, has accepted an appointment as Professor and Chairman of the Department of Medicine and Dean of the clinical faculties.

Dr. Charles C. Wolferth, F.A.C.P., Philadelphia, Dr. Virgil P. W. Sydenstricker, F.A.C.P., Augusta, Ga., and Dr. Harrison F. Flippin, F.A.C.P., Philadelphia, are members of the faculty of a refresher course for practicing physicians that will be offered by the Medical College of the State of South Carolina at Charleston, November 3–4.

Dr. Everett K. Geer, F.A.C.P., St. Paul, Minn., addressed the 30th Annual Meeting of the Mississippi Valley Conference on Tuberculosis and the Mississippi Valley Trudeau Society at Chicago, September 8–9, on the subject "Transient Infiltration of the Lung Parenchyma Associated with Eosinophilia."

Through the assistance of the Chinese Foundation, the Chinese Medical Journal, whose publication was suspended when the Japanese invaded Peking in December, 1941, has resumed publication on a quarterly basis in this country at P. O. Box 6096, Washington, D. C. It is said that printing and circulation facilities in Free China are inadequate, although the medical profession in China will still have its Chinese edition.

Dr. Charles Walter Clarke, F.A.C.P., Executive Director of the American Social Hygiene Association, New York City, has been named Clinical Professor of Public Health Practice at Harvard University.

Dr. James E. Paullin, F.A.C.P., President of the American College of Physicians and of the American Medical Association, addressed the Milwaukee County Medical Society, September 14; the Philadelphia County Medical Society and College of Physicians of Philadelphia, September 15; and the Michigan State Medical Society, September 22, at Detroit, on "The Responsibility of the Medical Profession in Post-war Planning."

Dr. Charles A. Doan, F.A.C.P., Professor of Medicine and Director of Medical Research, Ohio State University College of Medicine, Columbus, has been made President of the Ohio Public Health Association.

The State of Georgia has initiated annual registration of all licentiates of state examining boards. This began on September 1. No fees at present are required.

Some other states have long since initiated an annual registration. For instance, in Nebraska all physicians licensed to practice medicine are required by law to register with the Department of Public Welfare annually on or before October 1 and to pay a fee of $1.00. The license expires if the licentiate fails to register, but the license may be revived by the payment of the registration fee and a penalty of $1.00 within thirty days immediately after expiration.

Dr. Elihu S. Wing, F.A.C.P., Providence, has been made President-Elect of the Rhode Island Medical Society.

Dr. Ernest D. Hitchcock, F.A.C.P., Great Falls, Mont., as Chairman of Region 18, Montana and Wyoming, of the War-Time Graduate Medical Meetings, has conducted Graduate Conferences of two days' duration each at the Base Hospital, Fort Francis E. Warren, Cheyenne, Wyo., and at the Base Hospital at Great Falls, Mont. Subjects covered included anesthesia, clinical psychiatry, dermatology, radiology, and physical therapy. The faculty included Lieutenant George A. Bradasch, M.C., U. S. Army, Dr. Charles A. Rymer of the University of Colorado School of Medicine, Dr. Chester North Frazier, F.A.C.P., of the University of Texas Medical School, Dr. Leo G. Rigler of the University of Minnesota Medical School, and Dr. Frank H. Krusen, F.A.C.P., of the Mayo Foundation.

SPECIAL NOTICES

The Board of Trustees of the University of Illinois have announced the acceptance of a grant of $25,000 a year for three years made by The Upjohn Company of Kalamazoo, Michigan, to be devoted to the academic study of the structural composition and possible synthesis of penicillin.

The Company's present grant, says F. W. Heyl, Ph.D., Vice President and Director of Research, provides for an enlarged three-year research chemistry project under the direction of Professor Herbert E. Carter of the department of biochemistry at Urbana, Illinois. This, says Heyl, amplifies both an earlier coöperative research project at that school and the bacteriological and other research which is being conducted at the Company's laboratories at Kalamazoo.

Dr. Carter is well known for his brilliant work with the amino acids, especially the identification and synthesis of the new essential amino acid, threonine, and more recently for his investigations on the structure of the cerebroside sphingomyelin.

The production of penicillin by the natural growth of the mold *Penicillium notatum* is one of the most laborious and unsatisfactory methods in use for the manufacture of any known therapeutic agent. The hope of the future for the large scale economical manufacture of this important drug lies in the solution of the pure chemistry

which alone would lead to the chemical synthesis of the substance. It is in the hope of achieving this end that the Upjohn penicillin fellowship at the University of Illinois has been established.

This grant of The Upjohn Company is a good example of the greatly increasing scientific progress being made today in the chemical and pharmaceutical industries. It indicates the kind of investment in coöperative scientific research that must be made from time to time by leading organizations in these fields.

BETHUNE INTERNATIONAL PEACE HOSPITAL IN CHINA'S NORTHWEST MOVES THREE TIMES IN PAST YEAR TO ESCAPE JAPANESE. The Bethune International Peace Hospital, operating in China's guerrilla Northwest Territory, has been forced to move three times this year, according to a recent report from Mme. Sun Yat-sen to China Aid Council of United China Relief.

This hospital was driven out of its former permanent base at Wutaishan, in northern Shansi Province, in 1941, and since then has always been set up close to the fighting fronts, defying the sporadic Japanese mopping-up campaigns. Mme. Sun's report gives the hospital's present location as western Hopei Province, where it operates in scattered mud and brick peasant huts. This province is nominally "occupied" by the Japanese.

During the past six years, several International Peace Hospital doctors and nurses have lost their lives, but it is the boast of the hospitals' staffs that to date no patient has been lost or abandoned to the enemy.

This record is in part due to the volunteer-assistance of a permanent organization set up by local peasants in the Northwest and placed at the disposal of the guerrilla armies and the four International Peace Hospitals.

When approaching Japanese make hospital evacuation necessary, all resources of the surrounding villages are mobilized: horses, carts, carriers and stretcher bearers. Accompanied by nurses, the "convoys of wounded" are carried by primitive stretchers in relays from village to village. Branches of the peasant organizations meet them at each stop.

Village peasants also give valuable aid to the mobile medical and surgical units which go to within one half-hour's travel from the scene of fighting. Peasants help doctors to prepare operating arenas, set up sterilizing equipment, and to build temporary matsheds to shelter the wounded.

Women in the villages set up food kitchens and prepare dressings under the trained nurses of the medical unit.

Mme. Sun's report to the Council points out that more medical and surgical units are urgently needed. In the last period of active fighting, one mobile unit serviced three regiments, and handled as many as 300 cases of wounded a day. Mobile units can be maintained for $600 a year.

United China Relief, which financially aids the International Peace Hospitals, is a member agency of the National War Fund.

SELMAN FIELD, Monroe, La.—Capt. James O. Finney, chief of medical service at the Selman Field Station Hospital, has been promoted to the rank of major.

Major Finney was graduated in 1929 from Vanderbilt University and in 1933 from the university's medical school.

A native Alabaman, he resided at 509 Reynolds St., Gadsden, Ala., until he entered his current tour of active duty July 14, 1942. For six years he had practiced internal medicine in the Guice-Morgan Clinic in Gadsden.

Major Finney's military career began in Vanderbilt Medical school, where he was an ROTC student. He was commissioned in the Medical Reserve Corps when

he received his medical degree. He took his houseship in Vanderbilt University Hospital, at Nashville, Tenn., and did a year's postgraduate work at the University of Chicago. Then followed a five month tour at the Station Hospital at Ft. McClellan, Ala., after which the major began his practice in Gadsden.

A fellow of the American College of Physicians and a diplomate of the American Board of Internal Medicine, Major Finney has published several articles in the Journal of the American Medical Association, the Annals of Internal Medicine, the Southern Medical Journal and the Journal of the Alabama State Medical Association. Two of his papers have been reviewed in the International Medical Digest.

In 1934, Major Finney married the former Miss Margaret Pride, of Florence, Ala. The Finneys have two children.

Upon reëntering active duty in July, 1942, Major Finney spent a month as ward surgeon in the Station Hospital at Maxwell Field, Ala., and then was transferred to Selman Field.

A. C. P. REGIONAL MEETING, NORTH CENTRAL STATES

On October 16, the North Central States, including Illinois, Indiana, Iowa, Michigan and Wisconsin, held one of the outstanding regional meetings that it has been the fortune of the College to conduct anywhere. The formal program arrived too late to publish in the September ANNALS, but it is hereunder printed as a model program appropriate for these times.

PROGRAM

LeRoy H. Sloan, M.D., F.A.C.P.
Governor for Northern Illinois

Willard O. Thompson, M.D., F.A.C.P.
Chairman, Program and Arrangements Committee

Saturday, October 16, 1943

MORNING SESSION—8:30 a.m.

Ballroom, Drake Hotel

Presiding Officer

Cecil M. Jack, M.D., F.A.C.P., Decatur
Governor for Southern Illinois

"The Application of Graphic Training Aids to Medicine."
Ford K. Hick, M.D., F.A.C.P., Lieutenant Colonel, (MC),
U. S. Army, Chicago, Ill.

"Medical Experiences with the Navy in the Atlantic, Pacific and Caribbean."
James W. Sours, M.D., F.A.C.P., Lieutenant Commander, (MC),
U.S.N.R., Medical Officer V–12 Unit, Illinois Institute of Technology,
Chicago, Ill.

"The Five-Day Treatment of Early Syphilis."
Herbert Rattner, M.D., Assistant Professor of Dermatology,
Northwestern University Medical School, Chicago, Ill.

"Effort Syndrome in Soldiers."
Robert M. Moore, M.D., F.A.C.P., Clinical Professor of Cardiology,
Indiana University School of Medicine; Governor for Indiana,
American College of Physicians; Indianapolis, Ind.

"Personal Experiences in New Caledonia with Special Reference to Malaria."
    JAMES E. McFARLING, M.D., Captain, (MC), U. S. Army, Operations and
        Training Office, Camp Grant, Ill.

"Some Interesting Aspects of the 1943 Epidemic of Poliomyelitis."
    S. O. LEVINSON, M.D., Chairman of Advisory Committee on Infantile
        Paralysis, State of Illinois Department of Health, Chicago, Ill.

"Recent Advances in Chemotherapy with Special Reference to Penicillin."
    WILLIAM BARRY WOOD, JR., M.D., Professor and Head of the Department
        of Medicine, Washington University School of Medicine, St. Louis, Mo.

INTERMISSION

Presiding Officer

B. F. WOLVERTON, M.D., F.A.C.P., Cedar Rapids

Governor for Iowa

"Recent Advances in the U. S. Public Health Service."
    FRANK V. MERIWETHER, M.D., Medical Director, District No. 3,
        U. S. Public Health Service, Chicago, Ill.

"Some Clinical Observations on Meningococcic Infection."
    F. DENNETTE ADAMS, M.D., F.A.C.P., Lieutenant Colonel, (MC),
        U. S. Army, Consultant in Medicine, Fourth Service Command, Atlanta,
        Ga.

"Trauma to the Abdomen."
    WILLIS GATCH, M.D., F.A.C.S., Dean, Indiana University School of Medi-
        cine, Indianapolis, Ind.

"Functional Heart Murmurs."
    N. C. GILBERT, M.D., Professor of Medicine and Head of the Department,
        Northwestern University Medical School, Chicago, Ill.

"Personal Experiences in New Guinea."
    LEON S. EAGLEBURGER, M.D., Lieutenant Colonel, (MC), U. S. Army, Medi-
        cal Field Service School, Carlisle Barracks, Carlisle, Pa.

"Overseas with the Navy and Marines." (Illustrated by two short films.)
        (1) "The Medical Department in Amphibious Assault."
        (2) "Guadalcanal."
    WARWICK T. BROWN, M.D., Captain, (MC), U. S. Navy, First Marine
        Division, Bureau of Medicine and Surgery, Washington, D. C.

LUNCHEON

12:30 p.m.

Gold Coast Room, Drake Hotel

Presiding Officer

ELMER L. SEVRINGHAUS, M.D., F.A.C.P., Madison

Governor for Wisconsin

"Aviation Medicine."
    DAVID N. W. GRANT, M.D., F.A.C.S., Brigadier General, (MC), Air Sur-
        geon, U. S. Army Air Forces, Washington, D. C.

AFTERNOON SESSION—2:00 p.m.

Ballroom, Drake Hotel

Presiding Officer

ROBERT M. MOORE, M.D., F.A.C.P., Indianapolis

Governor for Indiana

"Recent Observations of Practical Significance on Gastric Secretion."
ANDREW C. IVY, M.D., F.A.C.P., Professor of Physiology, Northwestern University Medical School, Chicago, Ill.; Consultant in Naval Medical Research Institute, Bethesda, Md.

"Clinical Disturbances of the Pituitary."
EDWARD H. RYNEARSON, M.D., F.A.C.P., Assistant Professor of Medicine, Mayo Foundation, University of Minnesota; Consultant in Medicine. Mayo Clinic, Rochester, Minn.

"Classification of Hypo-estrinism."
FULLER ALBRIGHT, M.D., Associate Professor of Medicine, Harvard Medical School, Boston, Mass.

"Medicine Overseas."
HUGH J. MORGAN, M.D., F.A.C.P., Brigadier General, (MC), U. S. Army, Professional Service Division, Office of the Surgeon General, Washington, D. C.

INTERMISSION

Presiding Officer

P. L. LEDWIDGE, M.D., F.A.C.P., Detroit

Acting Governor for Michigan

"The Management of Carcinoma of the Colon and Rectum."
JOHN DE J. PEMBERTON, M.D., F.A.C.S., Professor of Surgery, Mayo Foundation, University of Minnesota; Head of Section in Surgery, Mayo Clinic, Rochester, Minn.

"War Neuroses."
DAVID SLIGHT, M.D., Professor of Psychiatry, University of Chicago, The School of Medicine, Chicago, Ill.

"Some Aspects of the Diagnosis and Therapy of Hypochromic Anemias."
OVID O. MEYER, M.D., F.A.C.P., Associate Professor of Medicine, University of Wisconsin Medical School, Madison, Wis.

The evening program included cocktails and a dinner meeting at which Dr. LeRoy Sloan, General Chairman, acted as the Toastmaster. The list of distinguished guests included official envoys from the offices of the Surgeons General of the Army, Navy and Public Health Service, of the Air Surgeon of the Army Air Forces, of the Deans and Professors of Medicine of the medical schools in the territory, of the Associate Directors of the American College of Surgeons, of the Editor of the Journal of the American Medical Association, of the Secretary of the Council on Medical Education and Hospitals of the American Medical Association, of the Presidents of the Institute of Medicine of Chicago, the Chicago Medical Society, the Chi-

cago Society of Internal Medicine, and the Illinois State Medical Society, of the Commanding Officers of the Ninth Naval District, the Great Lakes Naval Hospital, the Station Hospital at Fort Sheridan, the Sixth Service Command, and of the Office of Procurement and Assignment of the Sixth Service Command, as well as many other distinguished physicians and military officers. Brief addresses were made by Dr. Ernest E. Irons, President-Elect of the College, Dr. Charles Hartwell Cocke, 1st Vice President of the College, Mr. E. R. Loveland, Executive Secretary of the College, Commander Edward L. Bortz, Chairman of War-Time Graduate Medical Meetings, Dr. Morris Fishbein, and others.

OBITUARIES

DR. ORVILLE HARRY BROWN

In the death of Dr. Orville H. Brown of Phoenix, Ariz., which occurred in Arcadia, Calif., at the home of his daughter, one of the leading medical figures of the Southwest passed from the scene. For three years friends had witnessed with sympathetic astonishment his heroic struggle against the insidious and inevitable advance of a diffuse malignancy originating in the prostate. Dr. Brown's calm and philosophic acceptance of the situation is well illustrated by a personal report of his case, published in the Urologic and Cutaneous Review for June, 1942. In this attitude he was supported by the constant encouragement of his wife and daughter, as they together faced the situation with open eyes, but with courage and fortitude.

Dr. Brown was born in Kansas, July 18, 1875, and had, therefore, just passed his sixty-eighth birthday at the time of his death. He graduated from the University of Kansas, and then became assistant in physiology in that School for the years 1901 and 1902. He took part of his medical training at the University of Chicago while serving there as assistant in physiology from 1902 to 1904. He then went to St. Louis University School of Medicine, where he was assistant professor of pharmacology from 1904 to 1907, taking his degree in medicine there in 1905. In the same year he received his degree of doctor of philosophy from the University of Chicago.

From 1905 to 1907 he was associate director of the Mount St. Rose Sanatorium in St. Louis, and then became medical director of the Missouri State Sanatorium for Incipient Tuberculosis, at Mt. Vernon, Mo., which position he held from 1907 to 1910. During this period he made several notable contributions to the study of tuberculosis, both from the standpoint of individual treatment and from the aspect of public health. From 1910 to 1916 he was assistant professor of medicine at St. Louis University. During this period Dr. Brown carried out his study and research on asthma which culminated in the publication of his well known book on that subject in 1917, by C. V. Mosby Co.

In 1916, Dr. Brown moved to Phoenix where he spent the remainder of his professional life. For a time he was associated with Dr. W. O. Sweek

. as the internist of a medical-surgical team. In 1918 he was appointed Superintendent of Public Health for Arizona, holding this position until 1920. For approximately ten years, between 1920 and 1930, Dr. Brown practiced alone and became established as one of the leading internists of Arizona, giving special attention to asthma, in which field he was an acknowledged authority. In 1930 he formed an association with Dr. Loren C. Barlow, a surgeon, this affiliation being terminated suddenly by the death of Dr. Barlow in June, 1931, from epidemic meningitis. In 1932 Dr. W. L. Reid came as the surgical member of the Phoenix Clinic which was organized by Dr. Brown. Misfortune again struck when Dr. Reid was killed in an automobile accident in 1937.

He was an important figure in the Arizona State Medical Association and the Southwestern Medical Association. He was Editor of *Southwestern Medicine* from 1935 to 1940. In the Arizona Medical Association he held the important post of Historian for many years. He took this office seriously and devoted to it an enormous amount of time and energy. By untiring search through old newspapers and journals, by persistent correspondence with surviving members of families of doctors who had practiced in Arizona, and by personal interviews at every opportunity, he brought together and placed in the archives of the Association historical data regarding every doctor who has ever practiced medicine in the state. It was his ambition to prepare a "Medical History of Arizona," but this task now awaits the attention of some one else. Dr. Brown was elected to Fellowship in the American College of Physicians in 1931 and subsequently became a Life Member. He was a diplomate of the American Board of Internal Medicine, member of the American College of Chest Physicians, the American Association of Biological Chemists, and of the Royal Society of Medicine of London. He was the author of two books: one on "Laboratory Physiology" published during his early years in St. Louis, and the book on "Asthma" (previously mentioned), published in 1917. Besides these books he was the author (in a few instances in collaboration with others) of no fewer than eighty-five medical articles. His last published contribution was the personal account of his terminal illness,—"Two Years Experience With Bone Cancer."

Early in 1937, after the rather sudden development of urinary obstruction Dr. Brown had a transurethral resection done in Los Angeles and in the tissue removed evidences of prostatic carcinoma were found. He elected to be treated by the supervoltage x-ray equipment at the California Institute of Technology. The results seemed to be good and he continued his work. In 1939 the development of back pains, headaches and other symptoms led to investigation and he was found to have a very widespread metastatic involvement of osteoplastic type, in skull, spine, pelvis and ribs. Realizing the inevitable outcome of the situation Dr. Brown closed his office in June, 1940, and went with his wife to live with their daughter and son-in-law in Arcadia, Calif. With the spirit of a true scientist and philosopher, he offered

his case with its dramatic bone lesions, involving every vertebra in the spine and every rib, to the University of California for experimentation with irradiated heavy metals produced ·by the cyclotron. Under this treatment with irradiated strontium and phosphorus, much interesting and important data were acquired. Through the effect of this treatment, plus occasional treatments in Los Angeles by x-ray for pain, and his own personally directed dietary regimen, his life was prolonged from the maximum of three months set by Phoenix consultants (including the writer), to more than three years. During all this time Dr. Brown maintained his interest in professional work, writing several articles, reading many books and preparing book reviews for Southwestern Medicine, as well as making an intensive study of his own case.

His wife and daughter, facing the situation with equal courage, helped him maintain his cheerful and courageous philosophy to the end, when, undefeated and unafraid, he "wrapped the drapery of his couch about him and lay down to pleasant dreams." He was a good soldier. He fought a good fight. He kept the faith. Nothing better can be said of any man.

W. WARNER WATKINS, M.D., F.A.C.P.,
Phoenix, Ariz.

DR. ROBERT TITUS PHILLIPS

Dr. Robert Titus Phillips (Associate) was born in Boston, Mass., September 15, 1901, and died in a Japanese prison camp in the Philippine Islands, June 11, 1943; aged, forty-one.

He attended the Governor Dummer Academy, received his A.B. degree from Bowdoin College in 1924, attended the University of Edinburgh, Scotland, for one year, returning to Tufts College Medical School, from which he ·received his medical degree in 1932. He was an intern in 1932–34, and a resident physician from 1934–35, at the Boston City Hospital. Thereafter, he spent another year in residency at the Robert B. Brigham Hospital in Boston. He served as instructor in medicine at Tufts College Medical School, 1935–39; Junior Visiting Physician, Boston City Hospital, 1936–39; and as Assistant Physician at the Robert B. Brigham Hospital, 1936–39. He then removed to Portland, Maine, where he became a member of the staff of the Main General and Children's Hospitals.

Soon after the outbreak of World War II, he entered the Medical Corps of the U. S. Army as Captain. He was stationed in the Philippine Islands and was taken a prisoner of war at the ·fall of Corregidor. He was promoted to Major while a prisoner of the Japanese.

Dr. Phillips was a member of the Massachusetts Medical Society, the American Medical Association, the American Rheumatism Association, the American Congress of Physical Therapy, the New England Physical Therapy Society and the William Harvey Society. He had been an Associate of the American College of Physicians since 1937.

PENICILLIN AS A CHEMOTHERAPEUTIC AGENT *

By Martin H. Dawson, Gladys L. Hobby, Karl Meyer, and Eleanor Chaffee, *New York, N. Y.*

In 1929, while examining plates seeded with staphylococci, Fleming [1] observed that colonies failed to grow in the neighborhood of a colony of a contaminating mold. Following up this chance observation, Fleming isolated the mold, identified it as a strain of *Penicillium notatum,* and showed that it produced in broth cultures a soluble substance which exerted a remarkable inhibitory effect on pyogenic cocci and the diphtheria group of organisms but not on certain Gram negative rods. He designated the substance as penicillin and suggested that it might be used for differential diagnostic purposes in the cultivation of Gram positive and Gram negative organisms. He further suggested that it might be used as an antiseptic agent.

In 1932 Clutterbuck, Lovell and Raistrick [2] isolated a pigment produced by Fleming's strain of penicillium, but this substance proved to have no antibacterial action. Little further work was done on penicillin until 1940 when Chain and his co-workers [3] at Oxford, stimulated by the work of Dubos [4] on gramicidin, showed that crude preparations of penicillin exerted a remarkable effect in vivo against hemolytic streptococci, staphylococci and pathogenic anaerobes. In 1941 the Oxford workers greatly extended these observations and described a method for small scale production of material suitable for therapeutic use in man.[5] They further showed that penicillin was active in remarkably high dilutions, that it possessed little toxicity and that its action was not inhibited by blood, pus, or tissue derivatives.

The work reviewed in this paper was started in September 1940. Part

of it has been reported in detail elsewhere.[6, 7, 8, 9]   It constitutes a confirmation in part and an extension of the work of the English investigators.

Method of Preparation. Cultures of Fleming's strain of *Penicillium notatum* were grown in a modified Czapek-Dox synthetic medium for eight days at room temperature. After acidification and salt saturation of the culture fluid, penicillin was isolated by extraction with chloroform followed by distribution between aqueous solutions and organic solvents at different pH levels. It has been obtained either as a salt or as the free acid, the latter being more unstable than the salts. The free acid as well as a number of active acyl derivatives has been obtained in apparently crystalline form. Recently stable esters of penicillin have been prepared.[10, 11]

In Vitro Activity of Penicillin. Penicillin has been tested against a wide variety of Gram positive and Gram negative organisms. It is highly effective against Gram positive organisms, both aerobic and anaerobic, and

TABLE I

Susceptibility of Organisms to Penicillin

Susceptible Strains	Insusceptible Strains
Pneumococcus	*H. influenzae*
Streptococcus hemolyticus	*E. coli*
Staphylococcus albus	*B. typhosus*
Staphylococcus aureus	*B. dysenteriae*
Meningococcus	*B. proteus*
Streptococcus viridans	*B. paratyphosus A*
B. subtilis	*B. enteritidis*
Cl. welchii	*B. pyocyaneus*
V. septique	*B. fluorescens*
Cl. histolyticus	*B. prodigiosus*
B. sporogenes	Friedländer's bc.
B. oedematiens	*Staphylococcus albus**
B. sordellii	*Monilia albicans*
Lactobacillus	*Monilia krusei*
Cryptococcus hominis	*Monilia candida*

* Although staphylococci in general are sensitive to penicillin, a number of non-pathogenic *Staphylococcus albus* strains have been isolated which are completely resistant.

against gonococci and meningococci (table 1). Not all strains of the same organism are equally sensitive, but in general strains of pneumococci are more sensitive than strains of hemolytic streptococci, and the latter in turn are more sensitive than strains of staphylococci.

The action of penicillin appears to be either bactericidal or bacteriostatic, depending on the conditions of the experiment. It is active in extraordinarily high dilutions. Experiments with highly purified preparations of penicillin have shown that amounts as little as 0.03 microgram per c.c. are sufficient to inhibit the growth of a 10^{-2} dilution of a culture of hemolytic streptococci containing 200 to 300 million organisms per c.c. It is many thousand times as effective as any of the sulfonamides, its activity being comparable to that of gramicidin and tyrocidin.

The activity of penicillin was compared with that of gramicidin and tyrocidin in the following manner. Cultures of pneumococci, hemolytic

streptococci, and staphylococci were treated with similar concentrations of gramicidin, tyrocidin and penicillin. The cultures were incubated at 37° C. and the organisms per c.c. determined at intervals. The results show that the activity of penicillin is quite comparable to that of the other two substances tested (table 2).

TABLE II

Comparison of Penicillin, Gramicidin, and Tyrocidin in Vitro

Culture	Inhibiting Agent*	Number of Viable Organisms Per c.c.				
		0 Hr.	1 Hr.	3 Hr.	7 Hr.	24 Hr.
Pneumococcus (D/39)	Penicillin†	2,200,000	585,000	7,200	200	0
	Gramicidin	2,200,000	1,860,000	33,500	0	0
	Tyrocidin	2,200,000	0	0	0	0
Streptococcus hemolyticus (C203Mv)	Penicillin†	1,500,000	4,300,000	2,650,000	420,000	0
	Gramicidin	1,500,000	2,430,000	1,140,000	7,000	2,400
	Tyrocidin	1,500,000	100	0	0	0
Staphylococcus aureus (Oxford)	Penicillin†	7,750,000	13,900,000	700,000	73,500	0
	Gramicidin	7,750,000	490,000	2,400	0	0
	Tyrocidin	7,750,000	24,000	2,900	1,850	1,750,000

* 10 micrograms per c.c. of each used.
† Activity of penicillin preparation used in these experiments was approximately 100 Oxford units per mg.

Similar experiments were carried out with sulfathiazole and sulfanilamide. It was found that penicillin causes an actual diminution in the number of organisms, whereas sulfanilamide and sulfathiazole cause only a decrease in the rate of multiplication of the organisms (table 3).

TABLE III

Comparative Effect of Penicillin and Sulfonamides on Growth of Hemolytic Streptococci in Vitro

Drug 1 : 10,000 Dilution	No. Hours Incubation			
	0	4	7	24
Penicillin*....................	2,500,000	218,000	90,000	90
Sulfanilamide...................	2,500,000	10,100,000	65,000,000	20,900,000
Sulfathiazole...................	2,500,000	14,000,000	61,000,000	40,000,000
Broth Control....................	2,500,000	29,300,000	101,000,000	55,400,000

* A crude preparation containing approximately 500 Oxford units per c.c. was used in these experiments.

This is also illustrated by graph 1 in which the number of organisms per. c.c. is plotted against time. Further experiments indicated that the action of penicillin is not inhibited by blood or serum (graph 2).

In Vivo Activity. In vivo penicillin has an equally remarkable effect. Mice were infected intraperitoneally with a highly virulent strain of *Strep-*

tococcus hemolyticus and treated with small amounts of penicillin subcutaneously. The results of an early experiment with a crude preparation are shown in table 4. Animals were infected with amounts up to 2 c.c. of whole culture, containing at least 10 million lethal doses. The total amount of penicillin given to each animal was calculated to be approximately 7 mg. of the crude preparation, representing less than 350 Oxford units.[5] Sixty-six per cent of animals receiving 2 c.c. and 90 per cent of animals receiving 1 c.c
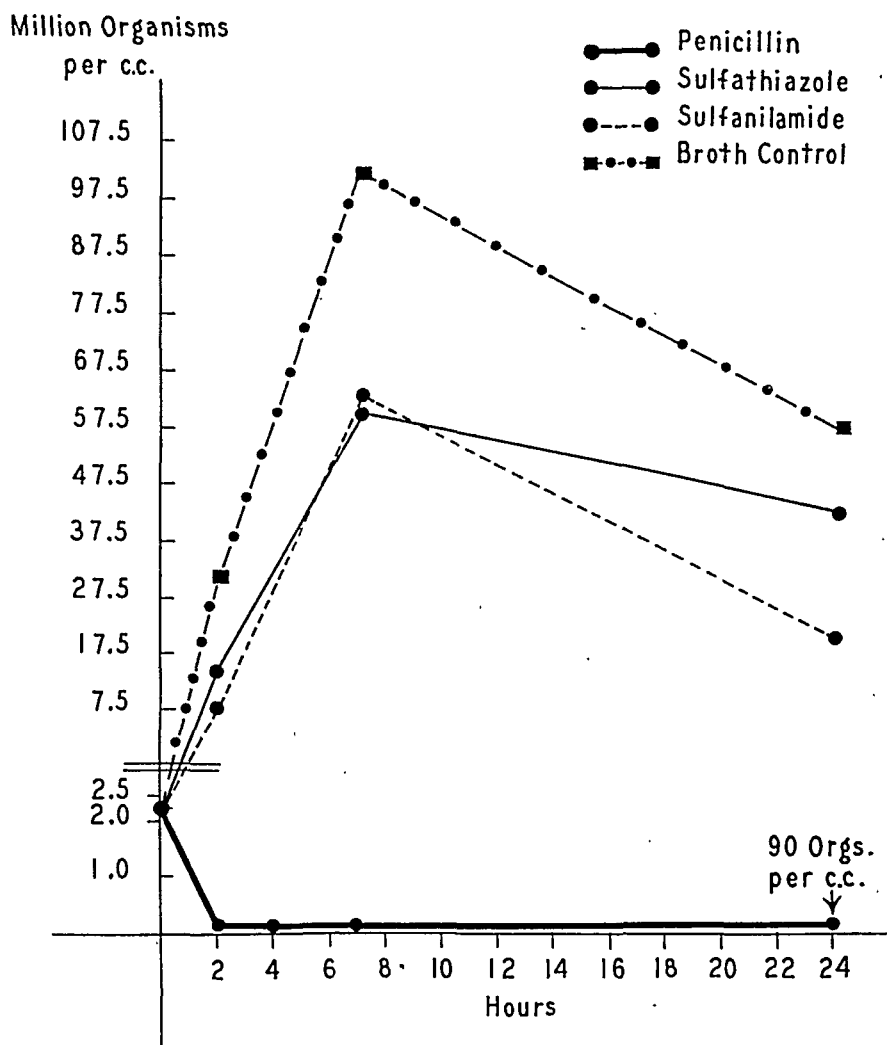
GRAPH 1. Comparative effect of penicillin and sulfonamides on growth of hemolytic streptococci in vitro.

of whole culture survived or showed prolonged life. Untreated controls receiving 1 c.c. of a 10^{-7} dilution all died within 48 hours.

In a subsequent experiment a titration of the activity of a more potent preparation of penicillin was carried out. It was found that 0.75 mg. of a preparation containing 150–200 Oxford units per mg. protected against 1 c.c. of a 10^{-2} dilution of a highly virulent strain of hemolytic streptococci (C203Mv)—(table 5).

In further experiments it was shown that penicillin is effective against hemolytic streptococcal infections when the penicillin is given intraperitoneally as well as when given subcutaneously.

In the experiments so far described treatment was instituted simultaneously with or shortly following infection. In other experiments it was
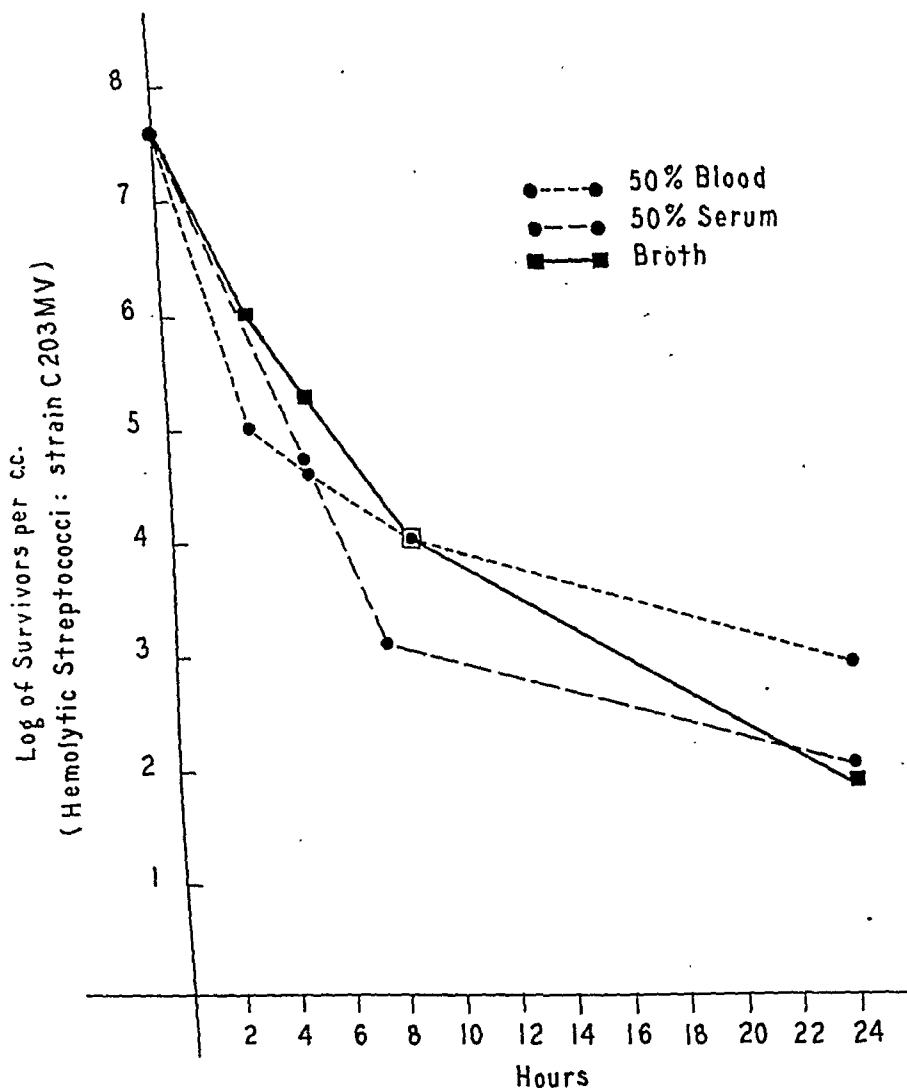
GRAPH 2. Effect of blood and serum on bacteriostatic action of penicillin in vitro.

found that mice could be successfully treated when the drug was administered as late as eight hours after infection.

Similar experiments were carried out on two strains of meningococcus Type I. The organisms * were grown on blood agar for six hours and then washed off into a small volume of physiological saline. This suspension was diluted with saline to a turbidity equivalent to a No. 1 MacFarland

* Meningococcus cultures were obtained from Dr. Hattie Alexander of the Babies Hospital, New York City.

TABLE IV

Effect of Subcutaneous Injection of Penicillin on Group A Hemolytic
Streptococcus Infections (C203Mv)

Dilution of Culture	Number of Organisms Injected (×1,000)	Number of Mice	Amount of Penicillin* (c.c.)	Number of Days Treated	Number Dead (<48 hr.)	Number Prolonged Life (2-7 days)	Number Survived (>7 days)
2.0 c.c.	180,000	9	0.4–0.65	<6	3	1	5
1.0 c.c.	90,000	10	0.4–0.6	<6	1	2	7
10^{-1}	9,000	15	0.2–0.58	<6	2	4	9
10^{-2}	900	13	0.2–0.57	<6	0	4	9
10^{-3}	90	11	0.2–0.57	<6	0	3	8
Controls 10^{-7}	0.009	15	0	0	15	0	0

* A crude preparation containing approximately 500 Oxford units per c.c. was used in these experiments.

Standard. Serial dilutions were made in 7 per cent mucin according to the method of Alexander [12] and 1 c.c. of a 10^{-3}, 10^{-4}, 10^{-5}, and 10^{-6} dilution injected intraperitoneally into a small series of white mice. Penicillin mixed with three volumes of sesame oil was given by the subcutaneous route ½ hour, 18 hours, and 24 hours after injection.

Although the number of animals is small, it is apparent that 1800 Oxford units of penicillin afforded almost complete protection against 10^{-5} and 10^{-6} dilutions of meningococci and partial protection against 10^{-3} and 10^{-4} dilutions. Untreated controls died in less than 24 hours (table 6).

Likewise, experiments were carried out on *Cl. welchii* and *Cl. septique* infections in guinea pigs. Cultures of *Cl. welchii* and *Cl. septique* * were grown in plain broth for 48 hours under anaerobic conditions and then

TABLE V

Titration of Activity of Penicillin * against Hemolytic Streptococci in Vivo

Dilution of Cultures	Penicillin (mg.)	Number Mice	Number Survived
10^{-2}	1.5	3	3
	1.0	3	3
	0.75	3	3
10^{-1}	1.5	3	3
	1.0	3	3
	0.75	3	0†
Undiluted	1.5	4	4
	1.0	4	2†
Controls 10^{-6}	0	10	Died <2 days
10^{-7}	0	10	Died <2 days

* Ammonium salt containing 150–200 Oxford units per mg.
† Two mice showed prolonged survival time in each instance.

* *Cl. welchii* (Strain 45) and *Cl. septique* (Strain 37) were used throughout. Cultures were obtained through the kindness of Dr. Frederick Humphreys of the College of Physicians and Surgeons, Columbia University, New York.

centrifuged. The cells were taken up in one volume of sterile distilled water and the suspensions heated at 80° C. for one hour. The resultant toxin-free suspensions were used in all animal inoculations.

Guinea pigs, weighing 300 to 350 grams each, were used for all experiments with *Cl. welchii*. White mice, weighing 18 to 20 grams, were found satisfactory for infection with *Cl. septique*. Equal volumes of spore suspension and of 10 per cent calcium chloride were injected simultaneously. All injections were given by the intramuscular route. Penicillin † treatment was started one hour after infection and was administered subcutaneously

TABLE VI

Effect of Penicillin on Experimental Infections Due to *N. meningitides*, Type I

Culture		Amount of Penicillin (Oxford Units)	Number of Mice	Number Died	Number Survived	Per Cent Survived
Strain	Amount					
Ombelet	10^{-3}	1,800	2	1	1	50
		0	2	2	0	0
	10^{-4}	1,800	4	2	2	50
		0	3	3	0	0
	10^{-5}	1,800	5	1	4	80
		0	3	3	0	0
	10^{-6}	1,800	5	0	5	100
		0	3	3	0	0
McNally	10^{-3}	1,800	4	1	3	75
		0	3	2	1	33
	10^{-4}	1,800	5	2	3	60
		0	3	2	1	33
	10^{-5}	1,800	4	0	4	100
		0	2	2	0	0
	10^{-6}	1,800	5	1	4	80
		0	3	3	0	0

once every 24 hours over a three day period. The penicillin used was dissolved in a small volume of saline and the solution mixed with three volumes of sesame oil. The dosage throughout was comparable to that which gives complete protection in mice against large infecting doses of virulent hemolytic streptococci.

Seventy-five per cent of the mice infected with 0.005 c.c. of a suspension of *Cl. septique* spores (approximately 1–2 MLD's) were protected by 434 Oxford units of penicillin. Approximately 50 per cent were protected against 0.01 c.c.–0.02 c.c. of such a spore suspension. No protection was obtained against 0.04 c.c.

All of the guinea pigs infected with 0.1 c.c. of a suspension of *Cl. welchii*

† We are indebted to Charles Pfizer and Company, Brooklyn, New York, for the penicillin used in these experiments.

spores (1–2 MLD's) were protected by the injection of 666 units of penicillin. There was no protection against 0.2 c.c. of spore suspension.

It is apparent that, whereas small amounts of penicillin protect against large numbers of highly virulent hemolytic streptococci, comparable amounts will give partial or complete protection against only two to three lethal doses of *Cl. welchii* and *Cl. septique*. The effect of larger amounts of penicillin on more severe infections by members of the gas gangrene group remains to be determined.

Toxicity. The toxicity of penicillin has been tested in mice, guinea pigs, rabbits, dogs and man. In addition, experiments have been carried out on tissue cultures and in the developing chick embryo. No toxicity was observed with amounts far beyond the range of therapeutic dosage.

For mice the LD_{50}, or the amount necessary to kill 50 per cent of the animals, was 12 mg. of the ammonium salt * † and 32 mg. of the sodium salt.† These amounts are equivalent to 0.666 and 1.8 grams respectively per kg. of mouse weight. Guinea pigs tolerated without visible effect as much as 320 mg. of the sodium salt—equivalent to 1.3 grams per kg. of guinea pig weight. These amounts are far beyond the range necessary for therapeutic dosage.

No toxic effects have been observed from penicillin in tissue cultures on the chorioallantoic membrane, or when applied directly to the human eye.[13] No untoward effects have been observed in man with doses up to 240 mg. or 60,000 Oxford Units of a highly purified product.

Absorption and Excretion. It has been shown that penicillin is absorbed after subcutaneous injection in mice, but that frequent administration is essential to maintain an effective blood level. Small amounts injected every two hours are more effective than large amounts injected at less frequent intervals. Studies on the bacteriostatic and bactericidal properties of the blood of treated animals indicate that penicillin remains in the blood stream for only two to three hours after subcutaneous injection.

Relatively pure preparations of penicillin, some in the form of the free acid and others in the form of the ammonium salt, were tested in rabbits. After intravenous injection of an amount calculated to be sufficient to give a blood level equivalent to three or four times the effective in vitro titer of the same preparation, activity was detected in the circulating blood for three to four hours but not longer.

Recently similar experiments have been carried out in man. Single injections of varying amounts of penicillin ‡ were given by the intravenous or intramuscular route. The bacteriostatic action of the blood was determined before and at various intervals after the injection of penicillin.

---

* The Oxford workers have stated that precipitation with dry NH_3 gas leads to inactivation of the penicillin. We have recovered penicillin quantitatively as the NH_4 salt as a routine procedure when moisture is rigidly excluded from the reaction mixture.
† These preparations contained approximately 200 Oxford units per mg.
‡ We are indebted to Merck & Company, Rahway, New Jersey, for the penicillin used in this experiment.

When penicillin is given by the intravenous route, there is a rapid loss from the blood stream during the first half hour after injection. The rate of disappearance from the blood stream then decreases, and the amount present falls off slowly over a period of two to four hours (graph 3). After this period no detectable amount remains in the circulating blood. These
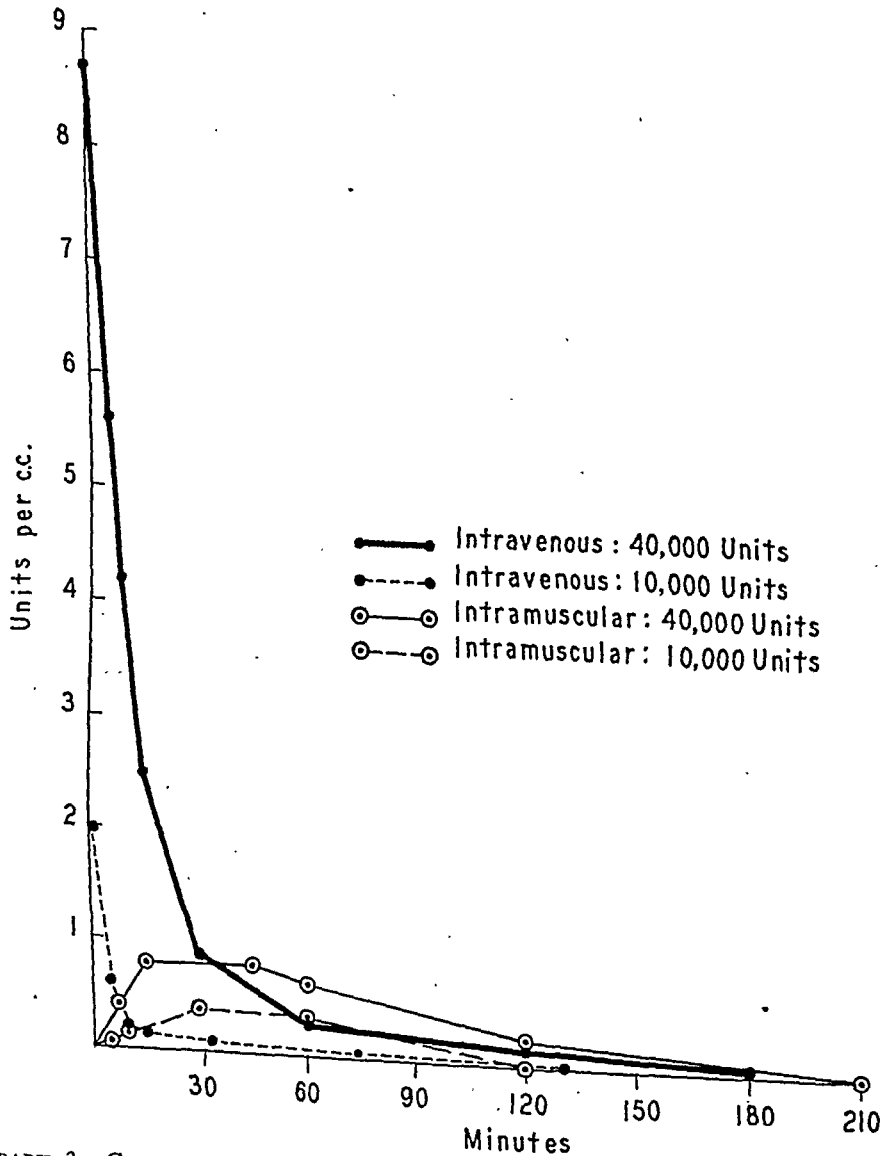
GRAPH 3. Composite curves showing amount of penicillin in blood after injection.

findings are in general accord with those reported by Rammelkamp and Keefer.[14, 15]

When penicillin is administered intramuscularly, the concentration in the blood stream reaches a maximum within 10 to 30 minutes. This level is maintained from one to two hours, after which time the amount present gradually decreases. After two to four hours penicillin can no longer be

detected in the circulating blood. Although the concentration in the blood is never as high after intramuscular injection, a higher level is maintained for a longer period of time.

The rapidity of excretion is a serious obstacle in the therapeutic use of penicillin. In animal experiments this difficulty has been overcome in part by the use of suspensions in oil and by the subcutaneous implantation of solid pellets. In such forms penicillin is absorbed and excreted less rapidly, and less frequent administration is necessary.[9] In the treatment of human infections, however, these procedures have not proved satisfactory. Efforts have therefore been directed toward the preparation of compounds which will slowly release active penicillin into the circulation. One of the authors (K. M.) has now succeeded in preparing such compounds. Their nature and use are described elsewhere.[10, 11]

Clinical Applications. Clinical use of penicillin has been greatly hampered by two facts: (1) the small yield, and (2) the desire to provide as much material as possible for chemical work. However, a number of cases have been treated with dramatic results. Penicillin has been proved to be effective in man when given intramuscularly, intravenously and intrathecally. It has also proved effective when administered directly into joints and serous cavities as well as in local applications. It is of value in the treatment of infections due to hemolytic streptococci, pneumococci, gonococci, meningococci and staphylococci. In particular, it has proved effective in cases resistant to sulfonamide therapy. The number of cases so far treated is small, but the results are highly encouraging. Up to the present time no serious toxic effects have been observed.

SUMMARY

Penicillin is a chemotherapeutic agent exhibiting a remarkable antibacterial action against Gram positive organisms and against gonococci and meningococci. It is not effective against Gram negative bacteria. Its activity is of a totally different order of magnitude from that of any of the sulfonamide compounds.

Penicillin is effective both in vitro and in vivo. It is active in the presence of pus and inflammatory exudates. Its action appears to be either bactericidal or bacteriostatic, depending upon the conditions of the experiment.

Penicillin appears to be completely non-toxic in doses far exceeding those necessary for therapeutic purposes.

Penicillin is rapidly excreted through the kidneys and frequent administration is necessary to maintain an adequate blood concentration.

Penicillin promises to be a chemotherapeutic agent of great clinical value.

BIBLIOGRAPHY

1. FLEMING, A.: On antibacterial action of cultures of a *Penicillium*, with special reference to their use in the isolation of *B. influenzae*, Brit. Jr. Exper. Path., 1929, x, 226.

2. CLUTTERBUCK, P. W., LOVELL, R., and RAISTRICK, H.: The formation from glucose by members of the *Penicillium chrysogenum* series of a pigment, and alkali-soluble protein and penicillin—the antibacterial substance of Fleming, Biochem. Jr., 1932, xxvi, 1907.

3. CHAIN, E., ET AL.: Penicillin as a chemotherapeutic agent, Lancet, 1940, ii, 226.

4. DUBOS, R. J.: Studies on a bactericidal agent extracted from a soil bacillus. I. Preparation of the agent. Its activity in vitro, Jr. Exper. Med., 1939, lxx, 1.

5. ABRAHAM, E. P., FLOREY, H. W., ET AL.: Further observations on penicillin, Lancet, 1941, ii, 177.

6. MEYER, K., ET AL.: On penicillin, Science, 1942, lxxxxvi, 20.

7. HOBBY, G. L., MEYER, K., and CHAFFEE, E.: Activity of penicillin in vitro, Proc. Soc. Exper. Biol. and Med., 1942, l, 277.

8. HOBBY, G. L., MEYER, K., and CHAFFEE, E.: Observations on the mechanism of action of penicillin, ibid., 1942, l, 281.

9. HOBBY, G. L., MEYER, K., and CHAFFEE, E.: Chemotherapeutic activity of penicillin, ibid., 1942, l, 285.

10. MEYER, K., HOBBY, G. L., and CHAFEE, E.: On esters of penicillin, Science, 1943, lxxxxvii, 205.

11. MEYER, K., HOBBY, G. L., and DAWSON, M. H.: Chemotherapeutic activity of esters of penicillin, Proc. Soc. Exper. Biol. and Med., 1943, liii, 100.

12. ALEXANDER, H.: Response to antiserums in meningococcic infections of human beings and mice, Am. Jr. Dis. Child., 1939, lviii, 746.

13. THYGESEN, P.: Personal Communication.

14. RAMMELKAMP, C. H., and KEEFER, CHESTER S.: The absorption, excretion, and toxicity of penicillin administered by intrathecal injection, Am. Jr. Med. Sci., 1943, ccv, 342.

15. RAMMELKAMP, C. H., and KEEFER, CHESTER S.: The absorption, excretion, and distribution of penicillin, Jr. Clin. Invest., 1943, xxii, 425.

REACTIONS TO PARENTERAL FLUID ADMINISTRATION *

By Max M. Strumia, M.D., John J. McGraw, M.D., and Alton Blake, M.D., *Bryn Mawr, Pennsylvania*

This review will discuss briefly the reactions to intravenously administered fluids in general, such as whole blood, plasma, human serum and crystalloid solutions. It will deal particularly with the question of reactions to plasma, since this material is now widely used and lately its rôle as an actual or potential source of reactions has been a controversial point.

The causes of reactions may be inherent in the fluid administered or may be conditions (physiological or pathological) peculiar to the recipient or to a combination of these two factors.

Some of the elements causing reactions, such as pyrogens, may be found in all of the fluids mentioned, whereas others are present or greatly prevailing only in certain fluids. Thus, hemolytic reactions have been reported practically only when erythrocytes have been administered. Often reactions are traced not to the fluid itself, but to improperly cleaned equipment used to prepare or administer the fluid. This is particularly true of pyrogenic reactions.

The most common reactions due to causative elements inherent in the fluid alone may be classified as pyrogenic, nitritoid, embolic or mechanical (from speed of administration). Reactions due to inherent qualities of the fluid combined with conditions of the patient may be listed as hemolytic and allergic. Conditions inherent in the recipient alone which increase the incidence of reactions may be listed as hyperhemolysis, liver disease, hypoproteinemia and cardiac insufficiency. Free hemoglobin, potassium content, temperature and air embolism are elements often mentioned as potential or actual causes of reactions which will also be briefly mentioned.

The hemolytic reactions following whole blood transfusion will be commented upon briefly in view of the fact that the subject has been covered by previous publications.

Pyrogenic Reactions

Pyrogenic reactions are by far the most common and may occur after the intravenous administration of any fluid which has been improperly prepared or administered with improperly prepared apparatus. Pyrogens, strictly speaking, are any substances which will provoke a febrile reaction after intravenous administration. Pyrogens are usually the product of bac-

terial growth and disintegration of bacterial bodies—certain bacteria, particularly gram negative varieties, produce more pyrogens than others.

The presence of pyrogens in poorly prepared or poorly preserved distilled water [1] and the ease with which glassware and apparatus become contaminated explain the relative frequency of pyrogenic reactions. In addition, blood, plasma and serum are relatively good media for bacterial growth, and a minimal chance contamination may be followed by bacterial growth sufficient to cause extremely severe reactions, when the material is used intravenously.

The pyrogen content of water varies considerably with the source from which it is obtained. It also varies with conditions favoring bacterial growth. Thus, still or slow-moving surface water, particularly in summer, may be expected to have a high pyrogen content whereas water from deep or artesian wells or spring water, protected from surface contamination, may be expected to be relatively pure. Practically all tap water contains pyrogens. These pyrogens cannot be removed or rendered harmless by sterilization by heat and they will pass through sterilizing filters. Co Tui and McCloskey, however, claim that it is possible to remove pyrogens by filtering through Seitz, No. 3 serum pads twice.[2] The only effective practical means of removal of pyrogens is by proper distillation. Proper distillation requires transforming the water to a pure dry gas followed by condensation to the liquid state.

Fresh properly distilled water is pyrogen-free and is often referred to as "parenteral." If distilled water contains pyrogens, it is usually due to one of three causes. First, the still or the container used to collect the distillate is contaminated. Second, the still is not properly constructed, so that droplets of water are entrained with the current of steam and carry pyrogens with them. Third, the water may be perfectly distilled but allowed to stand for several hours before sterilization so that bacterial contamination occurs. In addition, if the original water is heavily contaminated, the distillate is more likely to contain pyrogens. It is desirable, therefore, to start with as good a water as possible, and in all events to operate the still at a rate about half of the rated capacity. The water still must be equipped with a suitable trap or baffles to eliminate droplets of undistilled water. The still and storage chamber may be sterilized by running live steam through them each morning. Following this, the first 30 minutes, distillate should be merely considered a wash for the apparatus and discarded. No distilled water should be used after three to four hours unless it has been sterilized in a sealed container.

Pyrogenic reactions vary from very mild to extremely severe. The pattern is fairly constant. The reactions start within a very short time after the administration or during the administration, and consist of chill or temperature rise or both with a sense of malaise and occasionally nausea. The reaction is usually over in a few hours, very seldom lasts over eight hours. In extremely severe cases, high temperature is followed by circulatory col-

lapse. There is no satisfactory treatment of pyrogenic reactions, except symptomatic. Therefore, the remedy is prevention.

Human blood, plasma and serum do not originally contain pyrogens. They may, as stated, become contaminated if not properly prepared and preserved. These fluids do not lend themselves well to sterilization, although serum and, with proper procedure, plasma may be passed through sterilizing filters. This will not, however, remove pyrogens even if bacteria responsible for their production are removed. Filtration of blood or plasma with improperly prepared gauze filters or similar devices to remove fibrin flocculi is a not uncommon source of pyrogens.

The maintenance of such fluid as blood plasma and serum at refrigerator temperature (plus 2 to plus 8° C.) for relatively long periods of time slows, but does not eliminate the growth of certain bacteria. Likewise, the addition of mercurial antiseptics as bacteriostatic agents does not solve the problem. If these antiseptics are added in such concentration as to be fairly effective, the total amount of mercury may be too large when massive doses of plasma or serum are employed. If, on the other hand, the concentration of the antiseptic is low enough to avoid toxicity (merthiolate 1: 35,000, phenyl-mercuric-borate 1: 50,000), the presence of proteins in high concentration makes the action of the preservatives extremely doubtful. The addition of sulfanilamide [3] has not been found to be effective as was at first thought.[4]

Even careful bacterial studies are not an absolute assurance against severe pyrogenic reactions from this source in plasma or serum preserved in the liquid state. Only a small portion of such material, at best 2 per cent of the total volume,[5] is used in tests for sterility. Under such conditions, contamination with few bacteria may easily be missed, but subsequent growth of bacteria may cause very severe reactions.[6]

To guard against the formation of pyrogens in blood, plasma and serum it is necessary to take every precaution to prevent bacterial contamination. These precautions include asepsis in the collection of blood, and the preparation of plasma and serum by a closed method. A closed method is one which does not allow exposure to unsterile air at any time during the process.[7] In addition, plasma and serum should always be cultured and not released for use until proved sterile. It is not practical to culture whole blood since it would be several days old before results of cultural studies would be available. Citrated blood must be stored in a refrigerator at +2 to +4° C., immediately after collection and until used, to minimize bacterial growth if a chance contamination should occur. The period of storage should be as short as practicable. Plasma or serum for routine use should be stored in the frozen state. Storage in the frozen state will prevent bacterial growth. In the past, many transfusions of fresh blood have been given by an open method without excessive reactions. The reason is simply that the few bacteria which were contained in the blood were not given sufficient time to grow and cause reaction but if the blood had been stored, the organisms

would have multiplied and might have caused severe reactions. Preservation of plasma or serum in the dried state is also a safe method. Guarding against bacterial contamination of blood, plasma or serum does not of itself assure absence of pyrogens: glassware and rubber tubes must be pyrogen-free to avoid contamination.

It is possible, but not always practical, to test the pyrogenicity of plasma, serum and crystalloid solutions by animal injection. The results found in the animals, usually rabbits, are on the whole comparable to those found in man if a careful technic is followed.[8] The test is usually more apt to show a false positive than a false negative result. Distilled water may be chemically tested for presence of reducing substance.[9] A positive test indicates poor water but a negative test does not insure the absence of pyrogens. Distilled water may also be tested for its electrical conductivity. Here again a positive test (high conductivity) means poor water but a negative test (low conductivity) does not mean that pyrogens are absent.

The reactivity of both experimental animals and man to pyrogenic substances contained in fluids administered intravenously varies greatly. This is of importance both in testing solutions by inoculations in experimental animals such as rabbits and in evaluating pyrogenic reactions in man. When using rabbits for pyrogenic tests, the animals should be selected so as to eliminate both the hyper-reactive and the hypo-reactive.

Some patients will show no reaction to a given solution which may be mildly or moderately pyrogenic to other individuals. The amount and speed of administration also play a part. A small amount of mildly pyrogenic solution given slowly is not nearly so likely to cause a reaction as is a large amount given rapidly. Another obvious factor to be taken into account is the recipient's blood volume, which determines the final concentration of pyrogenic substances, all other conditions remaining constant.

Aside from the pyrogens contained in the fluid itself, there is another and perhaps even more common cause of pyrogenic reactions. This is the glassware and rubber tubing used to prepare and administer the material. Dirt and dust which may be allowed to collect in glassware may cause chill-fever reactions. Excess of sulphur which is found on most new compound rubber tubing may also cause reactions if it is not properly removed. All too often used bottles and tubing are allowed to stand wet for many hours under conditions favoring bacterial growth and then not adequately cleaned. Under such conditions pyrogenic reactions are the rule rather than the exception. The remedy is: (1) avoid contamination of the fluids remaining unused after administration; (2) proper cleaning of glassware and other apparatus, followed by rapid drying or sterilization; (3) distilled water should not be stored for over three hours after preparation unless sterilized.

With well prepared crystalloid solutions, the incidence of pyrogenic reactions is extremely small, less than one per thousand even with very large doses. With whole blood, the reactions of this type are more common, varying from 2 to 5 per cent. In well preserved plasma or serum they are

well below 1 per cent. Recovery is generally rapid and complete even in relatively severe reactions, save those followed by circulatory collapse.

In patients with a febrile temperature, especially if of the septic type, the intravenous administration of fluids, especially whole blood often causes a greater temperature rise. It is desirable in these cases, whenever possible, to administer the intravenous fluids at a time when the temperature is at its expected low, usually in the morning.

NITRITOID REACTIONS

These have been observed after administration of whole blood but are more common after the administration of freshly prepared serum or fresh serum which has been kept in the frozen state or dried from the frozen state. It has not been observed after the administration of crystalloid solutions. Usually the reaction immediately follows the administration of the fluid; in fact, it often occurs during the administration.

The reaction consists of a sense of constriction of the chest, often very alarming, pain over the lumbar region, sometimes, but not always, followed by chill and/or rise of temperature and occasionally by nausea, vomiting and headache. The reaction is usually over after a few hours (four to five hours) and appears to cause no permanent damage.

We have recently observed, through the courtesy of Dr. Angelucci and Dr. Minot, a patient who had severe reactions of the type here described following the administration of fresh whole citrated blood, and of dried pooled commercial plasma.

The patient, a 20 year old white girl, was suffering from severe anemia as a result of uterine bleeding. At 5 p.m. on June 8, 1943, she was given a transfusion of well matched group O blood, the patient also being group O and Rh positive. After 100 c.c. had been administered, the patient complained of an unusual feeling in the throat, tightness of the chest, and shortness of breath. The transfusion was stopped and was started again after symptoms had subsided. Cough and dyspnea became severe and the transfusion was discontinued. The patient was pale, nauseated and vomited. The pulse was weak, thready; the blood pressure was 130 mm. Hg systolic and 50 mm. diastolic. One hour after transfusion, the patient had a chill and the temperature rose to 104° F. The patient recovered promptly and the temperature returned to normal overnight. The blood had been collected in a commercial vacuum type bottle and was given immediately upon collection. At 11:30 a.m. on June 10, the patient received another transfusion of fresh whole citrated blood. After 10 to 20 c.c. of blood had been administered, the patient had a reaction similar to that reported above. A skin test with citrated whole blood and with plain sodium citrate was negative.

On June 18, the patient received a transfusion of citrated "lyophilized" plasma (Sharpe and Dohme) regenerated from the dried state. After only 10 c.c. had been administered, the patient complained of severe abdominal pains, accompanied by nausea and vomiting. Within one hour of the administration, there appeared a purpuric rash over the shoulders, arms and neck. The temperature rose to 103.6° F. The patient returned to her normal condition overnight. On July 9, the patient received a specimen of citrated blood obtained by gravity and with all possible precautions to avoid pyrogens. The blood transfusion was started at 11:30 a.m. at the rate of about 2 c.c. per minute. At 11:43 (when approximately 26 c.c. of blood had

been administered), the patient complained of abdominal discomfort, tightness of the chest accompanied by dyspnea and vomiting. The pulse became very rapid and weak; the systolic blood pressure increased from 110 to 138 mm. Hg and then gradually returned to 112 mm. Hg in a period of two hours, and the diastolic fell from 80 to 0 during the same period of time. This reaction was accompanied by chill and fever. Transitory cyanosis occurred about 30 minutes after the administration.

The patient was given saline and glucose solution repeatedly. Six hundred c.c. of saline containing 4 grams of sodium citrate were administered intravenously without reaction. On July 15 and July 17 the patient was also given washed red blood cells suspended in saline solution without reaction. On both occasions the red cells were those obtained from 500 c.c. of whole blood. The cause of reactions appears to be in the plasma itself.

These reactions have been observed after the use of very fresh serum but not after the use of serum which has aged for some time either at room temperature or at refrigerator temperature. Self and Scudder's recent work [10] tends to confirm these findings. It is therefore presumed that at least some of these reactions may be due to a substance or substances which are present in fresh serum and not in aged serum, or if present, in lesser amounts. It is further argued that since the intravenous administration of fresh plasma very seldom gives rise to nitritoid reactions, it is likely that the substance or substances responsible for at least some of the nitritoid reactions are a product of blood clotting. This was observed by Brodie as far back as 1900. [11]

For these reasons it is possible that one of the substances causing nitritoid reactions might be thrombin, which is formed in excess during the process of clotting. Investigative work is now in progress to determine the parallelism, if any, between the decrease of skin reactivity to intradermal injection of serum [12] and the decrease of thrombin content in a specimen of serum allowed to stand at room temperature.

Nitritoid reactions may not be entirely eliminated, but with the use of properly prepared whole blood or plasma they are sufficiently rare and relatively mild so that they need not constitute a major preoccupation.

EMBOLIC REACTIONS

Embolic reactions are not encountered in the administration of crystalloid solutions. These should not be filtered through paper or gauze, but through a sintered or fritted (glass) filter before sterilization. They need not be filtered again before administration. Whole blood should always be filtered immediately before administration. This is particularly important for blood preserved at refrigerator temperature for a period of time because of the rapid and progressive formation of numerous fine, soft flocculi.

Plasma and serum should always be filtered at the time of preparation, preferably at the time of pooling. If properly preserved thereafter, as mentioned below, they need not, strictly speaking, be filtered before administration. This is the practice which we have followed for a number of years [6, 13]

with plasma frozen immediately after pooling and filtration and maintained in the frozen state at — 20° C. or lower, and thawed before use in a circulating water bath at plus 37° C. To maintain this material free from flocculation, it must not be stored in the refrigerator after thawing, but kept at room temperature until used, as pointed out later. However, unless all steps of preservation and regeneration of plasma are under careful and dependable control, it is necessary to filter these fluids immediately before administration.

Embolic reactions so far have been rare. With plasma we know of only one case which seems fairly well established. This was brought to our attention by Dr. Cooksey of Detroit and by Dr. J. H. Lewis, who attended the patient.[6, 14] The patient, a boy, received 90–100 c.c. of undiluted, unfiltered plasma during a period of 20–25 minutes. Asphyxial death was sudden and occurred while the plasma was still being administered. This plasma had been separated from citrated blood by sedimentation for about 24 hours after collection of the blood. It had been preserved in the liquid state for 40–50 hours at refrigerator temperature. Microscopic examination of the lungs showed the smaller branches of the pulmonary artery to be plugged by a pinkish staining material, with a coarse reticular structure, closely resembling fibrin. Sections from other organs showed no such changes, presumably because the fibrin-like precipitates had not gone through the filter of the lungs.

The severity of this type of reaction and the ease with which it can be avoided should call everyone's attention to the elimination of any flocculi or fibrin precipitate. The most common cause of flocculation is the preservation of whole blood or plasma at refrigerator temperatures (2° to 8° C.). As far as whole blood is concerned, refrigeration is a necessity, and the only way to eliminate the danger of embolic reaction is carefully to filter the blood immediately before administration. However, flocculation of plasma may be entirely avoided by preserving plasma either in the frozen or dry state.

If plasma is to be kept in the liquid state for any period of time, it should be at room temperature, when flocculation does not occur for a period of four to six weeks and then very slowly. Flocculation may also be appreciably retarded in plasma by the addition of glucose solution.[15] Excessive dilution, however, must be avoided.

Effective filtration of flocculi, particularly thread-like precipitates of fibrinogen, is easily accomplished by the use of four layers of 40-mesh gauze, or equivalent material. The use of the standard 200 mesh stainless steel gauze is equally satisfactory, but quite expensive for generalized use. Good results have also been obtained by Dr. S. Brandt Rose[16] by the employment of a single layer of nylon cloth with 150–160 mesh per square inch.

Speed of Administration

Concerning the speed of intravenous administration of fluids, it is safe to state from practical experience and from the experimental work of

Altschule et al.[17] that if the concentration is isotonic, a rate up to 20 c.c. per minute is perfectly safe and well tolerated. However, this rate may be altered, either up or down, depending upon the need of more rapid blood volume replacement or the patient's cardiac condition. Thus, in patients in very severe shock, it is necessary to administer intravenous fluids, particularly plasma or blood at a much faster rate than that just mentioned. As much as 500 c.c. of material can be administered in a period of 10 minutes. Beyond this quantity, it is advisable to reduce the rate of administration.

On the other hand, in a patient in whom cardiac weakness is suspected, rates of fluid administration not exceeding 10 c.c. per minute should be advised. This is particularly true for the administration of whole blood because of its higher viscosity. Under these conditions, a rate of 5 c.c. per minute appears desirable. Within these limits it is reasonable to assume that the danger of reaction from speed of administration can be ignored.

However, excessive speed of transfusions must not be considered a source of reaction only through increased venous pressure. Speed is a very important factor in determining the rate and severity of transfusion reaction due to chemical factors contained in the transfusion fluid. Thus if pyrogens are present in a low concentration and the rate of transfusion is slow, no reaction may result. With increased speed, however, the concentration of pyrogens may at any given moment rise sufficiently to cause severe reactions. It is also to be noted that if the speed is slow, transfusion may be stopped, if necessary, before the reaction becomes too severe.

In at least two cases of transfusion of incompatible blood, in our own experience, fatal reactions were avoided probably because the rate of transfusion was slow and symptoms developed when only a relatively small amount of blood had been administered. This allowed the transfusion to be stopped in time to avoid more serious damage.

When not dealing with an emergency, therefore, administer the fluids at the slowest rate compatible with good results, generally not over 20 c.c. per minute. Patients should, as much as possible, be under observation when receiving intravenous fluids, particularly whole blood, plasma or serum.

HEMOLYTIC REACTIONS

Hemolytic reactions are comparatively rare but, because they are often fatal, it is important to take every precaution to avoid them. By far the great majority follow transfusion of whole blood into recipients whose plasma agglutinates the donor's cells. The possible rôle of the administration of plasma, serum and universal donor blood in producing hemolytic reactions will be discussed. Isotonic and hypertonic solutions of sodium chloride or dextrose have not been shown to cause such reactions. Theoretically a large intravenous infusion of distilled water should produce hemolysis, but Schemm[18] has reported at least two cases in which 1,000 c.c. of distilled water were unintentionally administered in the space of one hour

without adverse reaction. Similar occurrence should, of course, be carefully avoided.

In this paper a hemolytic reaction refers to the syndrome which follows the transfusion of incompatible blood. Blood is incompatible if the recipient's plasma agglutinates the donor's cells.

The typical hemolytic reaction starts during or very shortly after the transfusion. It commonly manifests itself by a chill, often followed by fever, nausea, vomiting, pain in the lumbar region and a sense of constriction in the chest. There may be abdominal cramps, pain over the bladder and an urge to defecate. Transient hemoglobinemia with passage of scanty reddish-brown urine is followed within five hours by hyperbilirubinemia, and shortly after by jaundice, usually reaching the peak within 24 hours. The oliguria may improve and the patient rapidly recover, but more often azotemia follows. This may lead to uremia and death or, after a period of several days when the issue is in doubt, the flow of urine increases and recovery follows. In a number of cases the patient may die even though the urinary output has become normal or even larger than normal. In these patients the nitrogen content of the urines is very low.

Laboratory examinations should be carried out to ascertain the diagnosis whenever a suspicion exists that a hemolytic reaction has occurred. The examination of the first urine passed after a hemolytic crisis reveals the presence of albumin, hematinic casts, hemoglobin and erythrocytes. A specimen of blood should be obtained immediately after the reactions and about five and 12 hours later. Hemoglobin in the plasma of the first specimen reveals that hemolysis has occurred. An increase in the bilirubin content of the second specimen as compared with the first further confirms the diagnosis. The peak of the bilirubinemia is generally reached between the fifth and the eleventh hours after the crisis.[19] Many theories have been advanced concerning the pathogenesis of the sequelae of the hemolytic reactions.[20] A critical review of these seems beyond the scope of this paper.

To our knowledge, there is no treatment which has proved uniformly successful. Alkalinization, renal decapsulation or sympathectomy, pelvic lavage, blood and plasma transfusion and many other procedures have been advocated. In any event, it seems logical to maintain an adequate fluid intake and an adequate blood volume.

The prognosis in any given case is somewhat difficult to determine. In general, in patients suffering from previous kidney damage or from any other serious illness, the outlook is unfavorable. The amount of blood administered seems to bear some relation to the end result. Most patients receiving 250 c.c. or less will recover from their first hemolytic transfusion reaction. Those receiving 500 c.c. or who have had previous transfusion reactions will usually die.

In view of the lack of any satisfactory treatment, it is absolutely essential to take every precaution to prevent hemolytic reactions. These precautions include a careful blood grouping of the recipient and the donor, care-

ful cross-matching tests, adequate studies regarding the anti-Rh and other less common isoagglutinins particularly in pregnant or puerperal women, and in persons receiving repeated transfusion. In addition, the transfusion should be given slowly so that it may be stopped early in the event of a reaction. Unfortunately, in some patients, the transfusion of incompatible blood is not followed by immediate reaction, and the first signs are passage of dark-colored urines and jaundice, followed by oliguria or anuria. It is our practice to use plasma as much as possible in place of whole blood, especially in emergency cases in which mistakes in blood grouping or matching may be the result of haste. There are very few patients who will not respond to plasma at least until a whole blood transfusion may be carefully planned.[6]

The preparation for a blood transfusion must be done by a well trained person. Adequately trained personnel must always be on call for such work.

The sera used for blood grouping must be of high potency. This means that blood grouping sera must be specific, of high titer and rapidly acting. They must be checked at regular intervals against cells of known groups. These cells are best obtained from thoroughly tested personnel of the hospital or laboratory. The anti-A serum must be capable of agglutinating the subgroups of A and AB. Checking the blood group by testing the unknown serum against known cells practically assures an accurate blood grouping.

Cross-matching should be done at room temperature and by incubating at 37° C. for half an hour as an aid in detecting agglutinins against such antigens as the Rh factor. Serum used for test tube cross matching should be inactivated to avoid hemolysis which might otherwise give the appearance of a negative reaction. All tests should be checked microscopically as well as macroscopically.

Women who are about to be delivered and who have had babies suffering with erythroblastosis and related syndromes, or who have just been delivered of such babies, will often show abnormal isoagglutinins which may be the cause of serious or fatal reactions unless special precautions are taken in the preparation for transfusion. For this reason all Rh negative pregnant or recently pregnant women should preferably receive Rh negative blood of proper group since the anti-Rh agglutinins may not be detectable in all instances even though the cross-matching is done at 37° C. and followed by centrifugation and examination.

When there is any reason to suspect a transfusion reaction, as in the case of pregnant women recently delivered of babies with erythroblastosis, patients with hemolytic anemia, liver disease, etc., it is well to resort to one of the so-called biological tests. We perform it by administering a 100 c.c. portion of the transfusion and comparing the serum bilirubin of the patient before and five hours after the test dose. If there is no reaction or rise in serum bilirubin beyond the experimental error of the test, it is safe to proceed. Wiener [21] has advocated a similar test which compares the color of the recipient's plasma or serum before and very shortly after the test dose. An increase in the hemoglobin content signifies hemolysis and warns against

completion of the transfusion. No change indicates that it is safe to proceed.

A more crude and not always effective test is simply to administer the transfusion very slowly in which case most reactions will be apparent before too large a quantity of blood is administered.

Plasma, serum and group O donor blood when administered to patients of other groups have been blamed as a cause of hemolytic reactions. The basis of these statements is the theory that the isoagglutinins present in plasma, serum or group O blood may occasionally be of sufficiently high titer [22] to clump and hemolyze the recipient's cells, and thus cause a serious or fatal reaction. Such a sequence of events is theoretically possible. However, the following case previously reported by one of us, suggests that such occurrence is unlikely, or at least, very rare.

A woman, aged 65, weight approximately 45 kilo., was suffering from carcinoma of the sigmoid with blood loss and secondary hypochromic anemia (3,750,000 erythrocytes per cu. mm.). She was given 280 c.c. of group A plasma which agglutinated her cells completely in vitro in a dilution of 1:320. The plasma was administered at the rate of about 6 c.c. per minute. No evidence of agglutination or of incompatible isoagglutinins was found in blood drawn from the opposite arm. The serum bilirubin did not rise above normal.

The adsorption or neutralization of isoagglutinins by the patient's erythrocytes and by dissolved A and B substances present in the plasma [23] does not seem fully to explain the absence of hemolysis in cases of the type reported above. When this patient's whole blood was mixed in vitro with an amount of plasma in proportion to the amount injected, agglutination and hemolysis occurred. A and B substances have been shown to be widely distributed throughout the body in most individuals. The rapid neutralization of isoagglutinins and iso-hemolysins is probably greatly aided by the A and B substances in fixed tissue cells.

The case reported above is not an isolated observation. No hemolytic reactions have been observed in over 4,000 administrations of unmatched plasma in our hospital. Most of this, however, was pooled and consequently had a low isoagglutinin titer. Elliot has had a similar experience using unpooled plasma but this practice is not advisable in view of Aubert's experience.[22]

Certain evidence has recently been put forward to the effect that isoagglutinins in plasma, serum and group O blood may cause hemolysis of the recipient's cells if the titer is sufficiently high. Aubert et al.[22] selected several human sera with an exceptionally high isoagglutinin titer and injected them into recipients of the opposite blood groups. They were able to detect evidence of hemolysis and agglutination in several cases. They noted agglutinates in blood drawn from the opposite arm after the transfusion. They also detected hemoglobinemia and a rise in the serum bilirubin up to 5 mg. per cent. A few recipients showed a drop in the total red cell count and hemoglobin. In this series no serum which had a titer of less than 1:512

produced any evidence of hemolysis. These workers concluded that sera of exceptionally high titer (1:512 or over) might produce hemolysis but that there was no danger from the use of the ordinary pooled material. This very important work should be repeated.

Pollayes and Squillace [24] reported a severe reaction to the intravenous administration of a single dose of commercially prepared lyophile plasma but the facts reported failed entirely to justify the conclusion that the reaction was hemolytic in nature.

It would be of particular importance to determine if there is any increase in the susceptibility to hemolysis in nonsecretors as compared to secretors.

Wiener and Moloney [25] recently reported the case of a woman belonging to group A who received group O blood after a postpartum hemorrhage. The plasma of the group O blood agglutinated the patient's red cells in high dilution. She had a hemolytic reaction but survived. The authors feel that it was the patient's cells that were hemolyzed since the donor's cells could be detected in the woman's blood for some time after the transfusion.

From all the work done to date, it seems justifiable to work on the assumption that serum, plasma or group O blood with an unusually high isoagglutinin titer may cause hemolysis of the susceptible recipient's cell in some instances. These reactions are very rare and can certainly and readily be avoided by pooling serum and plasma. We have never seen a pool of plasma with a higher titer than 1:32 when eight or more bloods were used to make the pool. Levinson and Cronheim,[23] and Davis and Meneely [26] have studied the isoagglutinin titer of pools of serum and plasma and they agree in general that pooled material does not have sufficient isoagglutinin content to be comparable in any way to the serum used by Aubert and his co-workers. More recently, Thalhimer [27] found that the titer of isoagglutinins in unselected pools of normal serum from all groups varied from 1:3 to 1:28. The number of individual sera in each pool varied from 10 to 49. Sophian [28] finds no evidence of hemolytic reaction from the use of plasma, and disagrees with the use of the expression "plasma shock." [29]

When using group O blood, it would seem desirable to be careful to avoid those bloods with excessively high isoagglutinin titers. Witebsky et al.[30] feel that this is unnecessary if purified A and B substances are added to the blood in order to neutralize the isoagglutinins.

Recently Levine and State [31] have stated that dissolved A and B substances in plasma seem to be a cause of reaction when given to patients of the opposite blood group. This would appear to be very unlikely, in view of the experience which we have had with the use of large amounts of unpooled plasma.[32] Elliott also has reported the use of unpooled plasma for several years without reaction.[33] Most of the plasma which we have used, however, has been pooled and the A and B substances presumably have been neutralized, in view of the fact that all pools tested have shown presence of some isoagglutinins.

ALLERGIC REACTIONS

Allergic reactions are usually attributed to substances of alimentary origin contained in the whole blood, plasma or serum to which the recipient is sensitive. They generally consist of localized urticaria with no systemic reaction. Less frequently, they consist of generalized urticarial manifestations with rise in temperature and occasionally with angioneurotic symptoms. Very rarely, a patient will develop an attack of true bronchial asthma during or after a transfusion of blood, plasma or serum. The possibility of edema of the glottis must be considered, but from all reports on hand, it is probably extremely rare.

It is impossible completely to eliminate these reactions which occur in 0.3 to 1 per cent of transfusions. One way to reduce them is to insist that the blood be obtained from the donor in a fasting condition. However, under ordinary conditions this is a difficult achievement in most institutions. The reactions are seldom severe enough to cause undue alarm and respond readily to epinephrine. True anaphylactic reactions following administration of whole blood, plasma or serum have not been observed by us.

JAUNDICE FOLLOWING TRANSFUSION OF WHOLE BLOOD, PLASMA AND SERUM

Occurrence of jaundice has been reported following the administration of certain yellow fever vaccines containing some human serum,[39] the intravenous administration of human serum [40] and of human whole blood and plasma.[41] The incubation period appears to be one to four months.

No definite etiologic factor has been demonstrated in such cases nor has it been established whether the donors of blood plasma or serum had had jaundice. Likewise, there is no proof of a relationship between the etiologic agent of infective jaundice and hepatitis and the icterogenic agent of blood serum and plasma.

Until more is known on this subject, it seems reasonable to presume that the icterogenic properties of blood and blood derivatives were due to a recent infection of the donor. In view of this, it appears reasonable to recommend that all prospective blood donors should be carefully questioned concerning a history of previous jaundice or contact with jaundice cases. A history of recent jaundice (within six months) or contact with such a case should disqualify a donor for blood transfusion.

HYPERHEMOLYSIS PREËXISTING IN THE PATIENT

Administration of well matched whole blood in patients suffering from hyperhemolysis from all sources but particularly in patients with hemolytic anemia is likely to cause a hemolytic crisis as pointed out by Greppi [34] and Sharpe and Davis.[35] We have observed the death of a patient suffering from hemolytic jaundice following the first transfusion of 500 c.c. of well

matched blood and in several other patients a severe hemolytic crisis. In these cases great care is to be taken to avoid such reactions by testing their "sensitivity" to the whole blood with a token transfusion of 100 c.c. in the manner already outlined. In any case, the rate of administration should be very slow, not to exceed 5 c.c. per minute. This procedure unfortunately is not practical in the newborn. In the icterus gravis neonatorum, extreme care must be exercised and the use of whole blood reserved for cases of extremely severe anemia. The conditions of shock and edema are effectively treated with plasma.

Liver Diseases and Hypoproteinemias

In severe liver damage, particularly if associated with jaundice, and in hypoproteinemias reactions to whole blood transfusion are more common than in the average case. Administration of whole blood should, in these cases, be done at a very slow rate and, in very severe cases, preceded by a test administration of 100 c.c. as already described. Whenever there is no severe anemia, plasma should be used in place of whole blood.

Cardiac Insufficiency

The administration of intravenous fluids, particularly those with high viscosity, such as whole blood, must be done very slowly in all patients with cardiac decompensation. With a rate not exceeding 5 c.c. per min. the danger of overburdening the heart is reasonably reduced to a minimum. The speed of administration in healthy individuals has already been considered.

Other Elements to Be Considered as Possible Causes of Reactions

Administration of small amounts of hemolyzed blood, such as contained in properly preserved blood, is to be considered harmless. As a matter of fact, intravenous administration of large quantities of crystallized or at least purified hemoglobin have been accomplished without apparent damage.[36] Likewise the danger from administration of small quantities of air trapped in tubing, connections and needles has probably been unduly emphasized[37]; however, it should be carefully avoided.[38]

The relatively high potassium content of preserved blood and of plasma prepared from such blood has been pointed out by Scudder[38] as a possible cause of reactions. In practice, however, no reaction has been observed even from administration of several liters of such material.

The administration of even large quantities of cold fluids intravenously does not cause reactions. In view of the fact that severe reactions, however, may follow administration of whole blood, plasma or serum which have been excessively heated, it is desirable to eliminate entirely the practice of warming transfusion fluids prior to administration.

There are some general precautions that greatly assist in reducing the rate of reaction to intravenous fluid therapy. These are briefly:

1. The preparations of crystalloid solution, the collection of blood, the preparation, preservation and administration of plasma, the cleaning assembly and sterilization of apparatus for intravenous fluid administration must be under a single centralized supervision, usually in connection with the clinical laboratory to secure proper standardization and control of each step.

2. A regular system must be instituted for the reporting in detail of all reactions occurring so that critical scrutiny of each case will allow improvement of the service.

BIBLIOGRAPHY

1. SEIBERT, F. B.: The cause of many febrile reactions following intravenous injections, Am. Jr. Physiol., 1924, lxxi, 621–651.
   RADEMAKER, L.: Cause and elimination of reactions after intravenous infusions, Ann. Surg., 1930, xcii, 195–201.
   RADEMAKER, L.: Reactions after intravenous infusions; further report on their elimination, Surg., Gynec., and Obst., 1933, lvi, 956–958.
   WALTER, C. W.: Preparation of safe intravenous solutions, Surg., Gynec., and Obst., 1936, lxiii, 643–646.
   WALTER, C. W.: Symposium on fluid and electrolyte needs of surgical patient; relation of proper preparation of solutions for intravenous therapy to febrile reactions, Ann. Surg., 1940, cxii, 603–617.
2. Co TUI, McKLOSKEY, K. L., SCHRIFT, M., and YATES, A. L.: New method of preparing infusion fluids, based on removal of pyrogen by filtration, Jr. Am. Med. Assoc., 1937, cix, 250–252.
3. NOVAK, M.: Use of sulfonamide derivatives as solution to problem of bacterial contamination in stored plasma, Jr. Am. Med. Assoc., 1942, cxviii, 513–515.
4. HEATH, F. K., and PROVINCE, W. D.: Preservation of human plasma; report of studies with sulfonamide compounds, Jr. Am. Med. Assoc., 1942, cxviii, 1034–1037.
5. National Institute of Health: Minimum requirements for unfiltered normal human plasma. Third revision, August 15, 1942. Bethesda, Maryland.
6. STRUMIA, M. M., and McGRAW, J. J.: Frozen and dried plasma for civil and military use, Jr. Am. Med. Assoc., 1941, cxvi, 2378–2382.
7. (a) STRUMIA, M. M., McGRAW, J. J., and REICHEL, J.: Preparation and preservation of human plasma; collection of blood and separation of plasma, Am. Jr. Clin. Path., 1941, xi, 175–194.
   (b) STRUMIA, M. M., and McGRAW, J. J.: Preparation and preservation of human plasma; drawing off, pooling and distribution of plasma, Am. Jr. Clin. Path., 1941, xi, 288–306.
8. National Institute of Health: Minimum requirements for unfiltered normal human plasma. Appendix A, August 15, 1942.
9. CARTER, E. B.: Proposed chemical test for pyrogen in distilled waters for intravenous injections, Jr. Lab. and Clin. Med., 1930, xvi, 289–290.
10. SELF, E. B., and SCUDDER, J.: The therapeutic use of serum and plasma, liquid and dried. In MUDD, S., and THALHIMER, W. (eds.): Blood substitutes and blood transfusion, 1942, C. C. Thomas, Springfield, Illinois, pp. 377–384.
11. BRODIE, T. G.: The immediate action of an intravenous injection of blood serum, Jr. Physiol., 1900–1901, xxvi, 48–71.

12. Strumia, M..M., and McGraw, J. J.: Report of Meeting of the American Human Serum Assoc., Williard Parker Hosp., N. Y., June 10, 1940.

13. (a) Strumia, M. M., and McGraw, J. J.: Preparation and preservation of human plasma; freezing of plasma and preservation in frozen state, Am. Jr. Clin. Path., 1941, xi, 388–401.
    (b) Strumia, M. M., McGraw, J. J., and Reichel, J.: Preparation and preservation of human plasma; drying of plasma from frozen state by low temperature condensation in vacuo, Am. Jr. Clin. Path., 1941, xi, 480–496.

14. (a) Strumia, M. M., and McGraw, J. J.: Development of plasma preparations for transfusions, Ann. Int. Med., 1941, xv, 80–88.
    (b) Mayner, F.: Death from transfusion of plasma, Jr. Am. Med. Assoc., 1941, cxvi, 2015–2016.

15. Elliott, J., Busby, G. F., and Tatum, W. L.: Some factors and observations on preparation and preservation of dilute plasma, Jr. Am. Med. Assoc., 1940, cxv, 1006–1008.

16. Rose, S. Brandt: Personal communication.

17. Altschule, M. D., and Gilligan, D. R.: Effects on cardiovascular system of fluids administered intravenously in man; dynamics of circulation, Jr. Clin. Invest., 1938, xvii, 401–411.

18. Schemm, F. R.: High fluid intake in management of edema, especially cardiac edema; details and basis of régime, Ann. Int. Med., 1942, xvii, 952–969.

19. Strumia, M. M.: Symposium on new trends in surgery; fate of transfused refrigerated blood and problem of blood banks, Surg. Clin. N. Am., 1942, xxii, 1693–1715.

20. DeGowin, E. L.: Grave sequelae of blood transfusions; clinical study of 13 cases occurring in 3500 blood transfusions, Ann. Int. Med., 1938, xi, 1777–1791.

21. Wiener, A. S., Silverman, I. J., and Aronson, W.: Hemolytic transfusion reactions; prevention, with special reference to new biological test, Am. Jr. Clin. Path., 1942, xii, 241–248.

22. Aubert, E. F., Boorman, K. E., Dodd, B. E., and Loutit, J. F.: Universal donor with high titre iso-agglutinins; effect of anti-A iso-agglutinins on recipients of group A, Brit. Med. Jr., 1942, i, 659–664.

23. Levinson, S. O., and Cronheim, A.: Suppression of iso-agglutinins and significance of this phenomenon in serum transfusions, Jr. Am. Med. Assoc., 1940, cxiv, 455–461.

24. Polayes, S. H., and Squillace, J. A.: Near fatal reaction to transfusion with dried human plasma solution, Jr. Am. Med. Assoc., 1942, cxviii, 1050–1051.

25. Wiener, A. S., and Moloney, W. C.: Hemolytic transfusion reactions. IV. Differential diagnosis: "Dangerous universal donor" or intragroup incompatibility? Am. Jr. Clin. Path., 1943, xiii, 74–80.

26. Davis, H. A., and Meneely, G. R.: Probability of obtaining potentially dangerous pools of serum or plasma, Science, 1942, xcvi, 468–470.

27. Thalhimer, W.: Intravenous injection of pooled normal plasma or serum; is it dangerous? Jr. Am. Med. Assoc., 1942, cxx, 1263–1267.

28. Sophian, L.: Toxicity of human plasma, Jr. Am. Med. Assoc., 1942, cxx, 860–861.

29. Editorial: Toxicity of human plasma, Jr. Am. Med. Assoc., 1942, cxx, 206–207.

30. Witebsky, E., Klendshoj, N. C., and Swanson, P.: Preparation and transfusion of safe universal blood, Jr. Am. Med. Assoc., 1941, cxvi, 2654–2656.

31. Levine, M., and State, D.: Skin sensitivity to human plasma, Science, 1942, xcvi, 68–69.

32. Strumia, M. M., Wagner, J. A., and Monaghan, J. F.: Intravenous use of serum and plasma fresh and preserved, Ann. Surg., 1940, cxi, 623–629.

33. Elliott, J.: Preliminary report of new method of blood transfusion, South. Med. and Surg., 1936, xcviii, 643–645.

34. Greppi, E.: I valori normali del recambio emoglobinico; l'indice emolitico, Arch. di pat. e clin. med., 1926, v, 459–478.

35. SHARPE, J. C., and DAVIS, H. H.: Severe reactions following transfusion in hemolytic jaundice; report of two cases, Jr. Am. Med. Assoc., 1938, cx, 2053–2056.
36. (a) SCHMIDT, J. E.: Untersuchungen über das Verhalten der Niere bei Hämoglobinaus-scheidung, Deutsch. Arch. f. klin. Med., 1907, xci, 225–239.
   (b) SELLARDS, A. W., and MINOT, G. R.: Injection of hemoglobin in man and its relation to blood destruction, with especial reference to the anemias, Jr. Med. Res., 1916, xxxiv, 469–494.
   (c) O'SHAUGHNESSY, L., MANSELL, H. E., and SLOME, D.: Haemoglobin solution as blood substitute, Lancet, 1939, ii, 1068–1069.
37. SIMPSON, K.: Air accidents during transfusion, Lancet, 1942, i, 697–698.
38. SCUDDER, J.: Shock: blood studies as a guide to therapy, 1940, J. B. Lippincott Co., Philadelphia.
39. The outbreak of jaundice in the Army, Circular Letter No. 95, S. G. O., Jr. Am. Med. Assoc., 1942, cxx, 51.
40. Homologous serum jaundice: memorandum prepared by Medical Officers of the Ministry of Health, Lancet, 1943, i, 83.
41. BEESON, P. B.: Jaundice occurring one to four months after transfusion of blood or plasma, Jr. Am. Med. Assoc., 1943, cxxi, 1332.

NUTRITION AND RESISTANCE [*]

By Fredrick J. Stare,[†] Ph.D., M.D., *Boston, Massachusetts*

The subject of nutrition and resistance raises the question of resistance to what—resistance to disease in general, resistance to specific diseases, resistance to therapeutic and toxic effects of drugs, etc. I shall review for you some of the more recent work on nutrition and various types of resistance.

Although it has been generally accepted that good nutrition is a requisite for a maximum degree of resistance to infection, it has been difficult to determine precisely what the relationship might be. It has been repeatedly suggested, for instance, that vitamins A and C are important in maintaining resistance, and the widespread popular acceptance of this idea is attested to by the tremendous quantities of these two vitamins sold each year in the perennial fight against the common cold. Such specific vitamin therapy as a prophylaxis against lowered resistance to infection has as a basis the many reports on vitamin deficiencies in animals and their susceptibility to infection, but convincing proof, especially as concerns human beings, has not been offered.

Thus, in the case of vitamin C, Sigal and King[1] and other investigators have demonstrated protection against the effects of diphtheria toxin afforded to guinea pigs by ample vitamin C intake, although the ability of vitamin C to assist in resisting diphtherial infection in the epidemiologic sense has not been demonstrated. Pinkerton and Bessey[2] found a loss of resistance to murine typhus in riboflavin deficient rats, and Badger, Masunaga, and Wolf[3] reported that thiamine deficient rats have an increased susceptibility to rat leprosy. Wooley and Sebrell[4] recently reported that mice fed less than the minimum requirements of riboflavin or thiamine for normal growth are more susceptible to intranasal inoculation with Pneumococcus type I than mice receiving amounts of these vitamins adequate to support normal growth.

Paired feeding experiments, wherein both the control and experimental groups of mice received the same amounts of food, clearly indicated that the increased susceptibility among the riboflavin-deficient mice was not due to malnutrition following anorexia. The daily administration of riboflavin or thiamine, in amounts five to 10 times that in the control diet, to the mice deficient in these substances at the time of inoculation with Pneumococcus type I, did not reduce the number of deaths.

Glazebrook and Thomson[6] reported the results of a study of the effects of ascorbic acid administration on resistance to infection in boys living in a large school in England. The work was done in 1938, at a time when distribution and particularly the serving of the food to the 1500 boys (15 to 20 years of age) was poorly managed. It was found that the total daily intake of vitamin C for each boy was only 10 to 15 mg. Urinary tests confirmed the serious degree of vitamin C depletion in these subjects.

The school population was divided into groups and occupied separate tables in the dining hall. Observations were made on the relation of vitamin C to infection by supplying some of the groups with the crystalline vitamin for several months.

The most frequent infections encountered were the "common cold" and "tonsillitis," the latter term being used as an index of hemolytic streptococcal disease of the nose and throat and included sore throat, otitis media, pharyngitis, and cervical adenitis. There was no difference in the incidence of the common cold between the control or vitamin C-treated groups. However, over a six month period, the boys in the control group spent an average of 5.0 days in the infirmary as compared to 2.5 days for the vitamin C-treated group. This difference was due to confinement caused by those infections classified as "tonsillitis," and in the incidence of other illnesses. There were 17 cases of pneumonia and 16 cases of acute rheumatism in the 1100 control boys, and not one case of either disease in the boys given ascorbic acid, though it should be pointed out that the control group had three times the number of subjects of the group given ascorbic acid.

This group of boys must represent a unique case since most studies of the general population indicate a much higher level of vitamin C intake than 15 to 20 mg. The results do not, therefore, justify ascorbic acid therapy in those already receiving "accepted" requirements. In fact, in a later communication, Glazebrook[6] emphasizes that these results must not be interpreted to mean that vitamin C plays a major rôle in resistance to disease.

Undoubtedly there is a wide variation in the "susceptibility" to hypovitaminosis C among individuals. Thus scurvy may first be indicated by a gingivitis, conditioned by local tissue susceptibility and improper oral hygiene. Likewise, anemia may be an early sign of scurvy, but it is conditioned by simultaneous suboptimal intake of iron. Thus, the individual with a latent vitamin C deficiency is placed in a precarious position against the attack of other disease-precipitating factors.

These considerations are undoubtedly important in interpreting the apparent conflict between the experiment of Crandon, Lund, and Dill[7] and the many reports on scurvy from other parts of the world. In the self-imposed scurvy produced in Crandon, the intake of other dietary factors was adequate and the subject was not exposed to other extraordinary natural conditions. Under these circumstances a great deficiency of vitamin C was required to produce certain signs of scurvy. Physical signs often associated with naturally-occurring scurvy, which may exist with less severe de-

ficiency of the vitamin, are undoubtedly precipitated by a variety of other conditions not experienced in the more controlled experiment.

Since it cannot be denied that some of our people are subsisting on inadequate diets, including low ascorbic acid intakes, these considerations and particularly the positive results of Glazebrook and Thomson require attention by health authorities in their efforts to prevent or lessen the disability caused by infectious diseases.

A recently reported investigation [8] on approximately 300 college students at the University of Minnesota showed no indication that either large doses of vitamin C alone or large doses of vitamins A, D, C, thiamine, riboflavin, and nicotinic acid together have any important effect on the number of infections of the upper respiratory tract when administered to young adults who presumably are already on a reasonably adequate diet. No nutritional studies were made but it seems reasonable to assume that these American college students were receiving a far better diet than the English boys reported in the previous study.

Reports on the relation of nutrition and resistance to disease are not confined to the effect of vitamin deficiencies. A recent report by Sako [9] presents investigations on the relation of protein, fat, and carbohydrate to "resistance to infection." In this study, young albino mice were fed diets varying in their content of protein, fat, and carbohydrate but with identical vitamin supplements. Growth on these diets was subnormal as compared with a stock diet, and growth on the low protein diets particularly was practically nil. After six weeks, the animals were injected with a standard multiple lethal dose of pneumococci and their survival time noted. Animals fed the high protein special diets survived longest; those fed the low protein diets died most quickly.

Dr. Paul Cannon [10] in his presidential address before the last meeting of the Association of Immunologists reviewed the importance of dietary protein for antibody formation. Cannon has shown experimentally that rabbits whose protein reserves had been reduced by low protein diets have a distinctly subnormal capacity to produce specific antibodies. This is in accord with evidence covering the increased susceptibility to infectious diseases observed along with inadequate diet during World War I. There is considerable evidence that an adequate dietary source of protein is of major importance in maintaining a high resistance, and it is appropriate to mention that the main protein foods are also the best sources of minerals and vitamins.

Somewhat in contrast with the work so far mentioned is the report of Feller, Roberts, Ralli, and Francis [11] in a different type of investigation on human beings in which they failed to demonstrate that vitamins A and C had any influence on: (1) the capacity of nasal secretions to inactivate influenza virus; (2) the titer in serum of neutralizing antibodies for influenza virus; (3) the activity of lysozyme in nasal secretions; (4) the titer of com-

plement in blood serum; or (5) the phagocytic activity of polymorphonuclear neutrophilic leukocytes for pneumococci. These studies were performed on normal human beings with diets adequate in calories and all foodstuffs except either vitamin A or C.

It is not possible to conclude, of course, that because these five immunologic phenomena were not influenced by changes in the blood plasma concentrations of the vitamins or by the degrees of deficiency attained, that vitamins A and C are not concerned with maintaining resistance to infection. However, these purely negative responses do emphasize the necessity for guarding against acceptance of a general conclusion that vitamins A and C have a specific function in "resistance to infection," particularly when the diet is adequate in other respects.

Changing the subject rather abruptly I should like to read part of an autopsy report[12]: ". . . arterial lesions consist of focal to extensive calcification, less often hyalinization or necrosis. These lesions were found in the lungs, heart, kidney, pancreas, thyroid, stomach, intestines, and mediastinum. Hyalin necrosis of skeletal muscle with or without calcification was found in all locations thus far examined. Lesions of the heart consist of necrosis of muscle followed by the formation of loose sparsely cellular scars. Slight to marked bone marrow aplasia (of granulocytes) was observed."

That is not an autopsy report of an elderly individual who died from the effects of a number of degenerative diseases, but of a young rat fed a diet adequate in all known nutrients but to which 1 per cent sulfaguanidine had been added to the ration. The above mentioned changes are completely prevented if yeast or liver is included in the diet. It is probable that sulfaguanidine inhibits the growth of certain intestinal bacteria which normally synthesize essential unidentified nutrients presumably belonging to the vitamin B-complex.

Intestinal bacteria are apparently of considerable importance to the nutrition of animals and of human beings. It is well known that vitamin K is synthesized by bacteria in the intestinal tract in quantities sufficient normally to meet the needs of man and most animals. Biotin, one of the vitamins of the B-complex, is provided to man in larger quantities by intestinal bacteria than by the diet.[13] Man may not develop deficiencies of biotin, pantothenic acid, pyridoxine, and other essential nutrients because these substances are made for him by microörganisms in the intestinal tract. But should the intestinal flora be altered, as by administration of drugs, diseases primarily nutritional in etiology may result.

We have been studying the relation of nutrition to the tolerance of daily administration of one of the synthetic antimalarial drugs. Experimentally in the rat, with carefully controlled purified diets furnishing good nutrition, we have not observed any remarkable pathologic changes. With the growing rat, daily administration of this drug inhibits growth. The extent of in-

hibition depends upon the amount of drug and the adequacy of the diet. Inhibition of growth due to the drug is additive to growth inhibition due to lack of certain essential nutrients. Thus, an animal on a diet partially deficient in riboflavin does not have a normal growth rate. If the drug is added to this partially deficient diet, its toxic effect is superimposed on the already ill effects of an inadequate nutritional state, and the animal is, therefore, in a more precarious position. Improvement of the diet by furnishing a normal amount of riboflavin will result in better growth but it will not prevent the growth inhibition due to the drug. It is probable that the same effect will be found with diets partially deficient in other nutrients. Therefore, because the toxic manifestation of the drug is additive to the effects of inadequate nutrition, it seems apparent that a good nutritional status, and an adequate nutritional intake, are important in tolerance to continued administration of certain drugs.

In summary, it may be stated that the diverse nature of the investigations on nutrition and resistance strongly favors a general conclusion, and a positive conclusion. The multiplicity of nutritive factors and pathogenic agencies used in the various studies suggests that a deficiency of any one of several nutrients may lead to a state of generally lowered resistance without any one factor bearing a so-called "specific" function. Many investigators have referred to the nonspecific nature of their findings. Certainly the experiments do not offer a rational basis for "overdose" therapy with any particular dietary factor, but they do justify accepting a strong relationship between nutritional well being and general resistance. And it is well to emphasize that nutritional well being is best obtained by an intelligent selection of foods of high nutritive value. The intelligent selection of foods of high nutritive value, so as to obtain in a quantitative manner a daily diet which really supplies the many nutrients necessary for good nutrition, cannot be left to the discretion of the average patient. Specific and accurate nutritional therapy should be a vital part of every physician's armamentarium.

Note. Since this address was given two interesting papers have appeared concerning nutrition and resistance. Trager [14] has reported that the blood level of biotin, one of the members of the vitamin B-complex, greatly influences the severity of avian malarial infection. Biotin-deficient chickens and ducks inoculated with large doses of *Plasmodium lophurae* showed peak parasite numbers 50 to 100 per cent higher than controls. The increased susceptibility in the biotin-deficient animals was not correlated with any general weakness resulting from the biotin deficiency. Older chickens which are more resistant to malarial infection showed a higher level of biotin in the blood than more susceptible younger chickens.

Smith, Lillie, and Stohlman [15] have studied the influence of dietary protein on the toxic effects of azobenzene, p-aminoazobenzene, and p-dimethylaminoazobenzene in rats. The degenerative liver changes and consequent impairment of liver function produced by these azobenzene compounds

are preventable by feeding high levels of good quality protein, particularly casein.

The author is indebted to NUTRITION REVIEWS for permission to use some of the material presented in this paper.

BIBLIOGRAPHY

1. SIGAL, A., and KING, C. G.: The influence of vitamin C deficiency upon the resistance of guinea pigs to diphtheria toxin, Jr. Pharmacol. and Exper. Therap., 1937, lxi, 1–9.
2. PINKERTON, HENRY, and BESSEY, OTTO A.: The loss of resistance to murine typhus infection resulting from riboflavin deficiency in rats, Science, 1939, lxxxix, 368–370.
3. BADGER, L. F., MASUNAGA, E., and WOLF, D.: Leprosy: vitamin B deficiency and rat leprosy, Pub. Health Rep., 1940, lv, 1027–1041.
4. WOOLEY, JERALD G., and SEBRELL, W. H.: Nutritional deficiency and infection. I. Influence of riboflavin and thiamin deficiency on fatal experimental pneumococcal infection in white mice, Pub. Health Rep., 1942, lvii, 149–161.
5. GLAZEBROOK, A. J., and THOMSON, SCOTT: The administration of vitamin C in a large institution and its effect on general health and resistance to infection, Jr. Hyg., 1942, xlii, 1–19.
6. GLAZEBROOK, A. J.: Vitamin C and resistance to infection, Brit. Med. Jr., 1942, ii, 617.
7. CRANDON, JOHN H., LUND, CHARLES C., and DILL, DAVID B.: Experimental human scurvy, New England Jr. Med., 1940, ccxxiii, 353–369.
8. COWAN, DONALD W., DIEHL, HAROLD S., and BAKER, A. B.: Vitamins for the prevention of colds, Jr. Am. Med. Assoc., 1942, cxx, 1268–1271.
9. SAKO, WALLACE S.: Resistance to infection as affected by variations in the proportions of protein, fat, and carbohydrate in the diet, Jr. Pediat., 1942, xx, 475–483.
10. CANNON, PAUL R.: Antibodies and the protein reserves, Jr. Immunol., 1942, xliv, 107–114.
11. FELLER, A. E., ROBERTS, LESLIE B., RALLI, ELAINE P., and FRANCIS, THOMAS, JR.: Studies on the influence of vitamin A and vitamin C on certain immunological reactions in man, Jr. Clin. Invest., 1942, xxi, 121–137.
12. ASHBURN, L. L., DAFT, FLOYD S., ENDICOTT, K. M., and SEBRELL, W. H.: Lesions in rats given sulfaguanidine in purified diets, Pub. Health Rep., 1942, lvii, 1883–1891.
13. OPPEL, THEODORE W.: Studies of biotin metabolism in man. Part I. The excretion of biotin in human urine, Am. Jr. Med. Sci., 1942, cciv, 856–875.
14. TRAGER, WILLIAM: The influence of biotin upon susceptibility to malaria, Science, 1943, xcvii, 206–207.
15. SMITH, M. I., LILLIE, R. D., and STOHLMAN, E. F.: The toxicity and histopathology of some azo compounds as influenced by dietary protein, Pub. Health Rep., 1943, lviii, 304–317.

PSYCHOSOMATIC ILLNESSES IN URBAN PRACTICE *

By R. S. Leadingham, M.D., F.A.C.P., *Atlanta, Georgia*

Psychoneuroses with their attendant autonomic alterations of visceral functions frequently assume the pattern of organic disease and become major problems in identification and management. When they are associated with frank morbid anatomical processes they create confusion in diagnosis and often lessen the effectiveness of therapy. Economically, their significance is not generally recognized, although if valid statistics were available they would rank high among the causes of inefficiency and days lost from employment, to say nothing of the added cost of medical care. One patient for 10 years set aside 50 dollars a month from a small income for medical services, and the drug bill of another amounted to 25 per cent of her monthly salary. They are responsible for a large number of rejections of selectees for military service and constitute a considerable percentage of patients in base hospitals at the present time. They vitally affect every phase of our social life.

Physicians looking for "real pathology" are apt either to overlook the significance of psychosomatic complaints or to be impressed with the apparent futility of trying to effect a cure. However, more interest is being shown by medical and social agencies now than ever before in the identification of their causes and management of treatment. This interest has been stimulated by the general advance of medical science, better preparation of medical students, better teaching in medical schools, and by the increased public interest in making responsible medical care available to all classes of society. We hear and read more about treating the individual and not the disease; about the contrast between viewing the patient as an entity and the individual with some specific form of disease. And as society is thrust upon the threshold of an era of increased social responsibility that must be shared by the whole social order, religion, science, business enterprise, and government, it will become increasingly obvious to the public how vitally social and economic problems affect the individual's well-being and how much bodily pain and metal anguish may be caused by their wrong evaluation. We may then, as clinicians, frankly accord to psychopathology the same importance given to organic pathology in alterations of physiological functions common to both conditions.

Psychosomatic disturbances are no respecters of persons. They affect the high and the low, the rich and the poor, and the sick and the well. They have their origin, unquestionably, in inherited and acquired traits. The age

incidence of episodes is from the time of early self-determination to death. No race or sex is immune and the influences of party or creed are negligible. The specific etiologic factor appears to be a virus of inadequacy adapted to the human race from its beginning. It is spread by contact and fomites of commonplace intellectual and emotional practices.

The effect of the virus is upon the central nervous system, and somatic symptoms appear with the involvement of the autonomic portion. However complicated its connections may become, the reflex arc in one form or another is the physiological unit which forms the basis of most, if not all, nervous activity. The centers of such complex phenomena as consciousness, intelligence, judgment, memory, speech, and other phases of symbolic thought, of which little is known, lie within the aggregations of cells constituting the cerebral cortex where reflex action may still be simple enough to be analyzed, as in the case of conditioned reflexes, or so complicated as to be lost in the maze of human behavior. There are direct paths leading from this mantle of consciousness to the midportions of the brain where are located the autonomic centers with control over elemental functions which respond directly to cortical stimuli.

Patterns of thought and autonomic response are fashioned in early life and become more inflexible with the passing years. Into these molds are poured the ideas and experiences that form the personality society recognizes. The effect of psychic trauma upon these patterns will depend upon their degree of flexibility and upon the nature and amount of the casting material. The manifestations of trauma are manifold. They may be behavioristic or somatic or both. The symptoms are variable, transient or prolonged. The physiological reactions to fright may be present in any form whether due to fear of body harm or to anxiety from any cause. With the conditioning of time they may not be obvious except in acute exacerbations. Somatic symptoms may vary from transient elevation or lowering of arterial pressure to complex manifestations of aberrant physiological processes that constitute definite clinical syndromes. Sometimes a single organ system is involved and at other times a number may be affected. The circulatory and alimentary systems frequently present the most annoying symptoms. Tachycardia, extrasystoles, and alterations in blood pressure are the most common cardiovascular symptoms. Dysphagia, anorexia, distention, nausea and vomiting, hyperchlorhydria, pain and tenderness in the epigastrium or moving from place to place in the abdomen, constipation or diarrhea, mucous colitis and the "spastic colon" are gastrointestinal symptoms.

The respiratory rate may be quickened. There may be dyspnea on exertion, smothering sensations, or frank attacks of bronchial asthma. An interesting phenomenon in respiratory tract involvement is the quickened deep breathing that leads to hyperventilation and its attendant feelings of dizziness, faintness, and unreality. These sensations can readily be demonstrated to the patient when he is recounting his experiences by having him breathe deeply and frequently by the watch.

The genitourinary symptoms include increased or decreased libido, impotence, dysuria, frequency, perineal and lower abdominal and lumbar aches and pains.

Altered functions of the ductless glands may be indicated by prolongation of the menstrual cycle, missed periods, overactivity sometimes with hyperplasia of the thyroid gland and alterations of the blood sugar curve.

The most frequently observed cutaneous manifestation is simple erythema. Increased response to intradermal tests for allergy and especially to histamine often causes confusion in diagnostic procedures.

Frank nervous symptoms may arise from the upper or lower segments of the nervous system. Peripheral nerve pain, paresthesias, anesthesias, hyperesthesias of the skin are common. From the higher centers come the signs of hypersensitivity to suggestion and unusual awareness of visceral activity, as the heart beat and peristaltic movements of the gastrointestinal tract. Headache, fatigability, restlessness, and sleeplessness are among the earliest complaints, and then follow the travails of indecision, poor judgment, faulty memory, etc., as parts of the phenomena of psychic disorder.

Psychosomatic symptoms may appear as an anaphylactic phenomenon in emotional shock. They occur also as manifestations of repeated, less severe psychic traumas. It is interesting to note how often an individual pattern is presented. In one individual the blow is felt upon the gastrointestinal tract, in another the cutaneous nerves bear the onus, in another the ductless glands, in another the circulatory system in the form of extrasystoles or hypertension, and in another if the patient suffers from bronchial asthma, acute exacerbations may be precipitated at a time when specific therapy should have controlled the paroxysm. A familial tendency is also occasionally observed. A young woman whose chief complaint was frequency of urination, voiding once or twice an hour during the day, stated in her family history that her father and three brothers were "nervous" and had "kidney trouble."

The prognosis in these cases depends upon the severity and duration of the illness. Transient symptoms of emotional shock where the cause is obvious respond readily to treatment. The prolongation of symptoms and their interpretation as evidence of organic disease may fix them in the consciousness of the patient. In some instances the purely psychic symptoms may be relatively few and obscured by localized complaints as pain over McBurney's point, dyspepsia, constipation, etc. Then the essential causative factors may be most difficult to determine. With the passing of time, the individual tends to make more involved adjustments on the basis of his inadequacy and chronic invalidism may result.

Resistance to the disease varies with and within the individual. The defense mechanism involved is analogous to the mechanism giving us acquired immunity to infections. Acquired immunity to infectious disease is produced by the body's response to repeated subclinical irritations or by a sustained effort which eventually overcomes an infection and establishes a

defense against microbial invasion. For a short period in early life the mother's immunity protects her child, during which time normal parasites take up their abode upon and within the infant's body. The colon bacillus flourishes in the alimentary canal, the staphylococcus upon the skin, and the streptococcus in the oral cavity. Kept within proper confines, they cause no harm and a communal relationship is established between parasites and host. Repeated minor invasions of the staphylococcus build up an increased resistance of the body against the time when an injury may allow a large number of these organisms to enter its tissues. The colon bacillus frequently invades the urinary tract. Filtrable viruses injure the mucous membranes of the nasopharynx allowing the organisms of the mouth to produce the common upper respiratory infections. These minor infections condition the body for future invasions of larger numbers or more virulent bacteria. As in all natural defense phenomena the conditioning process is variable and unpredictable.

Likewise, in the realm of social experiences, maternal influence protects the child. Later, by repeated contacts at home and school, at work and play, in making a living or making of friends, throughout life, the impact of human relations enhances or impairs the effective life of the individual. Lasting immunity may ensue from devastating personal experiences but, in the main, if we live out our life expectancy, our happiness and usefulness depend upon a varying state of immunity or hypersensitivity to the impacts of every day living. As with somatic infections, the outcome of each episode will depend upon the number and character of the impacts and the individual's resistance to them. Wherever the blows may fall, and whatever the complexes may be, the symptoms express an exaggerated normal reaction to fear. Some reactions of childhood may persist throughout life, and others result from experiences of the present or immediate past. Upon their conditioning depends the body's response to the intrusion of deleterious influences.

No doubt the most important influence shaping the child's pattern of response is parental example. Guidance by church and school stands little chance of being effective in homes torn by dissension or controversy about the child's behavior. Later experiences in love and plans for a career place upon many unprepared shoulders heavy weights of responsibility. The effect of indecision, of inordinate ambition in adolescence, may be felt for years afterward. Religious experiences, business and professional associations, family cares and marital incompatibility, physical handicaps, and social delinquencies are commonplace contributing factors in adult life to the development of feelings of inadequacy and symptoms of autonomic nervous system imbalance. In order to determine the nature and seriousness of these influences, considerable understanding, time, and patience are required. The attitude and preparation of the first physician to prescribe for the physical manifestations of stresses will greatly influence their outcome. If he is unaware of psychic factors involved, or, for any reason, fails to

enlighten his patient about the nature of his complaints and directs his attention solely to the amelioration of presenting symptoms, fear of sickness and death may be added to an already burdened mind. Mention of findings such as a heart murmur, a two plus Wassermann, questionable peptic ulcer, or a retroflexed uterus, may be taken to heart and accepted as evidence of the physician's desire gently to break the news of impending disaster. From such fears arise some of the most painful anxiety states which may be made worse by unnecessary, even though well-intentioned, medical or surgical treatment.

Clinically, these patients can be placed in three empirical groups:

First—the acute exogenous group. Individuals who suffer from stresses that would properly place burdens upon right-thinking persons, as the concern of a sick mother for a wayward son, the sudden awakening of a man to the hazards of a new undertaking, broken love affairs, and the sudden facing of major health problems.

Second—the social welfare group. Individuals whose difficulties are due to repeated or constant friction in home, business, and social affairs.

Third—the personal habit group. Individuals whose faulty habits of thinking and behavior cause them to feel inadequate for normal social and business life, including abnormal sex practices, excessive use of alcohol, drug and prescription addicts.

The problems of the first group present little difficulty in diagnosis and, with the proper appreciation of causes, are amenable to sympathetically administered palliatives and the assistance of family and friends.

In the second group constituting a large number with prolonged symptoms, it becomes necessary to secure more information than can be obtained from the patient for the identification of offending circumstances. Not infrequently the conduct of other members of the family or poorly advised business associates needs more attention than does the patient. Here the physician may find himself confronted with a problem for which he has little time or preparation, and it is with this group that the trained social worker can render the most assistance in diagnosis and treatment. Many are borderline psychiatric cases.

The third group demands psychiatric skill well recognized in modern medical practice.

Treatment of the first two groups includes psychotherapy, medical treatment, and prophylaxis. Whether the general practitioner or the specialist in any branch of medicine desires to, or not, he has to accept responsibility for the identification of psychosomatic disturbances and their management, personally or by reference. Care and time spent in history taking prevent many headaches in evaluating physical findings. The patient with psychosomatic symptoms unrelated to organic pathology usually will give an involved history if permitted to do so, although specific complaints may be the only ones brought out at the first visit to the physician. Therefore, an hour or more

given over to the patient's recital without direct questioning may not be wasted and will save valuable time and unnecessary reëxaminations later. Physical examination necessarily must be carried out according to the problem presented with full appreciation that physiological alterations caused by psychic disturbances produce discomfitures, and that the patient may not be telling a falsehood when he states he has a pain in his epigastrium, numbness of his extremities, or dyspnea on exertion, even though there may exist no morbid process to account for these symptoms. Remedial measures other than conversation are best withheld until a degree of harmony between history and physical findings can be established in the minds of patient and physician regardless of time consumed. When symptoms occur to complicate somatic disease, strict attention to obvious pathologic lesions until their cause may be ascertained, will obviate much difficulty later. The effect of sedatives may be likened to that of opiates administered to a patient with a questionable surgical abdomen, and the resulting hazards in diagnosis and treatment are frequently as comparable. In fact, any medicine given before the nature of the illness is known may give the patient a false sense of security and lead him to believe or hope that his illness may be primarily attributable to some physical cause.

Inasmuch as many symptoms are associated with such obvious physiological abnormalities as hyperchlorhydria, hypo- or hyperthyroid activity, abnormal glucose tolerance curves, spasticity of the gastrointestinal tract or altered arterial pressure, the question naturally often arises about what medicinal or other therapeutic measures are indicated for the alleviation of such conditions. When it can be made plain to the patient that it is to his interest to remove the cause of his trouble, it does not matter much what crutches are used if they are not allowed to become habit forming, or the means by which he may punish himself for his lapses. Basal metabolic rates will return to normal, blood sugar alterations will disappear, and the colon will lose its spasticity as he gets his balance and faces the world with more poise and confidence. In well developed cases he must learn to expect relapses, and, until he can make a total adjustment, he must be satisfied if they recur less frequently and are of shorter duration. On the other hand, patients with confirmed psychosomatic disease may become ill with essential hypertension, renal colic, coronary disease, peptic ulcer, frank mental disease, and all other physical afflictions common to man. Likewise, prolonged illnesses may be complicated by emotional stresses and their accompanying trains of psychosomatic symptoms.

I believe most psychiatrists are of the opinion that many, if not most, of the cases of the first and second group, if properly handled, will fare better in the hands of the family physician than in their own. Certainly in the majority of instances the individual simply needs the doctor's moral support for a period of time, with the minimum of therapy, or material assistance from sources prepared to give it. Many cases, however, do become psychiatric problems, especially where diagnosis and treatment at the hands of

their physician have shown lack of appreciation of factual causes. The frequent necessity of adapting a patient's personal life to strictly somatic illnesses unquestionably accounts for many failures to recognize and properly care for psychosomatic disturbances. There is, however, little question but what the medical profession has often erred in considering the patient the doctor's property, and has extended the patient-physician relationship to the point where mysticism born of wishful thinking has been substituted for the realistic approach of scientific medicine. We may admit our responsibility for much unscientific rationalizing that has impeded the progress of medicine and frequently evoked the scorn of our critics. One factor in unscientific rationalizing is the difficulty of obtaining valid social histories from individuals who are loath to see any connection between psychic stresses and physical discomfitures when perhaps the causes of the stress are commonplace practices or occurrences for which many of their acquaintances appear to find satisfactory compensations. Another source of error lies in the exploitation by laity and profession of tonics, sedatives, hormones, and vitamins as panaceas for emotional disturbances, and the unwarranted assumption that physical fitness, especially in relation to the ductless glands, insures emotional stability. We deal with human beings, not tokens of scientific, economic, or social progress. And in the pursuit of truth, the human mind has not invariably passed by graded steps from witchcraft to metaphysics, and from metaphysics to science, but has grudgingly accepted, by the painful process of trial and error, every new contribution made for human betterment. Moreover, many individuals appear to be unable to accept these contributions and at the same time realize that they follow, and do not invalidate, the natural laws shaping human progress.

Lack of time and training frequently renders the physician's task of determining the source or solution of the patient's troubles very difficult. When they arise entirely, or in part, from misfortune or ineptitude in daily living and faulty family adjustments, social agencies in the larger cities are equipped to assist by making investigations and recommendations the physician cannot undertake. The fact that these agencies accept responsibility often has a very salutary effect upon disturbing elements in certain cases.

Each physician should have his own manner of approach after having determined something of the nature of contributing causes. Confidence in his own ability and forthright interest in the patient's welfare can ordinarily be demonstrated in the same manner in which he would refer a patient to a surgeon, internist, or orthopedist. But to the lay mind these illnesses often bear a stigma more distasteful or fearful than did cancer, syphilis, or tuberculosis, three decades ago. Therefore, patience, and not abruptness, sympathy, or disgust, should keynote the physician's advice and the patient should be made to understand what benefits might be expected from such reference. Much might be said about the manner in which cases needing the attention of psychiatrist or social agency can be brought to want the assistance they provide.

The importance of prophylactic measures has been given little direct attention except in the field of child psychology; yet it should be obvious to any interested observer that although a pattern may be formed in childhood, it does not follow that childhood experiences necessarily account for all emotional disturbances developing in adult life. We find sources of disturbances in every field of human endeavor, and if we in this democracy are to fulfill the obligation we believe is ours, to produce not human robots or intellectual frankensteins, but confident, clear thinking, free men and women, we must, in this period of the world's history, coördinate all our efforts in church, business enterprise, science, and government, not alone to salvage human waste, but to safeguard the ideals we profess. Only the physician is in position to accept responsibility for the individual as a biological entity in a social world in matters pertaining to his physical and mental health, but in the broader sense illnesses of all kinds are community and public health problems.

Increasing emphasis upon the validity of diagnostic criteria and upon the axiom of proved medical practice, i.e., to remove the cause is to effect a cure, demands, where possible, closer coöperation of the medical profession and social agencies. We may then apply the same interest in determining specific causes for psychosomatic complaints as is shown in the identification of febrile illnesses, heart disease, or the evaluation of symptoms of the surgical abdomen, and to institute suitable measures of relief for the cases in which major social problems are involved. We may be able, also, better to evaluate the factors in our national economy contributing to their production.

THE EFFECTS OF NOVOCAIN INJECTIONS ON SIMULATED VISCERAL PAIN [*]

By Dennison Young, M.D., *Tallahassee, Florida*

Peripheral manifestations of nerve root involvement in spondylitis have been known since the days of von Bechterew,[1] but it was not recognized until many years later that similarly radicular pain secondary to hypertrophic or infectious arthritis of the spine [2, 3, 4, 5, 6] or narrowing of the intervertebral spaces [7, 8] could mimic intrathoracic disease or acute abdominal emergencies. The usual treatment of this type of pain has consisted of various drugs, physical measures including baking and massage, manipulations of the affected joints, and often roentgen-ray therapy. Unfortunately most of these measures yield but transient relief and frequently the pain has persisted or recurred soon after treatment was stopped. For these reasons it has been thought worth while to try the effects of novocain injections on a group of patients in whom pain simulating visceral disease was the result of paravertebral muscle involvement, secondary to spondylitis.

Local or regional injection therapy for muscle pain is not new. Its origin has been traced back to the time of the Tsin period about 300 A.D.[9] Since then the beneficial effects of injection of many substances into varying locations for the relief of low back pain and sciatica have been described. Kellgren [10, 11, 12, 13, 14] first demonstrated that in a certain number of patients with simulated visceral pain, pressure over the paraspinal muscles adjacent to a localized kyphosis reproduced the pain and injection of large amounts of 1 per cent novocain into this area abolished the symptoms for varying periods of time. Similar observations have been reported by Harman and Young [15] in patients with "rheumatic" lesions of the deep back muscles but no spinal involvement.

During the past two years 26 patients with spondylitis and simulated visceral pain, in whom the symptomatology could be reproduced by pressure on the muscles lateral to one or more vertebrae and by torsion or hyperextension of the spine at the same level, were subjected to a similar procedure. The cases fell readily into groups:

1. Those with simulated visceral pain and no organic visceral disease.
2. A larger group with visceral disease and simulated visceral pain due to somatic disease.

In the first group, symptoms frequently were referred to the abdomen, often "renal colic," although "pseudo-angina" was also encountered. Clinical and laboratory studies always failed to reveal organic visceral disease, but all patients displayed the characteristic findings: tenderness immediately

lateral to one, two, or three dorsal or lumbar vertebrae, reproduction of the abdominal or thoracic complaint on pressure at these sites and on forced motion of the spine, and radiographic evidence of a spondylitis at the same level.

The second group was composed chiefly of patients with organic heart disease and "pseudo-angina." Many had been followed for years with anginal symptoms believed due to the cardiac disease but with no response to the usual therapeutic measures. Points of tenderness to the left of the lower cervical and upper and mid-dorsal spine were always present and pressure and manipulation at these sites reproduced exactly the "anginal syndrome." Radiographically, hypertrophic changes in the vertebrae were observed, except in those patients with rheumatic fever and acute or subacute spinal involvement. A negative roentgenogram does not, however, preclude the diagnosis of spondylitis. Parker and Adson [10] have shown pathologically that hypertrophic changes resulting in cord compression may exist for a considerable period of time without their radiographic recognition.

CASE REPORTS

The following cases are illustrative of group 1.

Case 1. R. N., a 46 year old female, stated that for six months prior to admission she had suffered from intermittent episodes of severe, sharp precordial pain frequently radiating into the left arm and usually occurring after heavy exertion. There was no clinical or laboratory evidence of cardiovascular disease. Marked muscle tenderness immediately to the left of the bodies of the ninth and eleventh dorsal vertebrae was elicited and pressure at these sites reproduced exactly the spontaneous pain. Neurologically, hyperesthesia to pinprick from D9 to D12 was present on the left posteriorly and over the anterior left hemithorax. The left breast was markedly tender on pressure. Radiographic examination showed a moderate degree of hypertrophic spondylitis.

Eight c.c. of 2 per cent novocain were injected at each of the two tender sites and about two hours after the injection the pain was completely gone. The following day neither the hyperesthesia nor breast tenderness was present and the patient stated that for the first time in six months she had been able to sleep on the left side and not awaken due to paroxysms of pain. She was still free from pain 11 months after the injection.

Case 2. M. N., a 54 year old female, for three months prior to admission suffered from steady severe low-back pain radiating down the buttocks. During the preceding week she had experienced three attacks of severe right loin pain radiating anteriorly and downward into the groin. These were believed by her physician to be renal colic and each required several injections of morphine for relief. Because of this she was admitted to the hospital for urological investigation. Examination revealed tenderness to the right of the first lumbar vertebra and over both sacroiliac synchondroses. Pressure and forced motion at the lumbar site produced pain similar to the previous acute "renal colic," and pressure over the sacroiliac articulations caused severe low-back pain radiating down the buttocks. Ankle jerks were absent and there was decreased sensation to pinprick of the lower extremities from the knees down. The urine was negative and urological investigation revealed no evidence of urinary tract disease. Roentgenogram of the spine showed an advanced degree of

hypertrophic spondylitis of the dorsal vertebrae and slight changes in the lumbar region.

Ten c.c. of 2 per cent novocain were injected into the paravertebral muscles to the right of the first lumbar vertebra and 15 c.c. at the upper margin of each sacroiliac joint. The following day she was markedly improved. On the second day she felt even better, no longer experiencing pain on changing from the recumbent to the sitting position nor on walking. There was no further radiation of pain anteriorly. Eight months after injection, she was free from all pain and had had no further episodes of "renal colic."

The following cases illustrate results achieved in group 2.

Case 1. S. M., a 60 year old female with known hypertension and hypertensive heart disease for seven years and thyrotoxicosis of three years' duration, complained of sharp, intermittent, knifelike pain in the lower left anterior chest for the past two months. These had been considered anginal in nature but had not been relieved by nitroglycerine. Examination revealed typical findings of hyperthyroidism and hypertensive heart disease with auricular fibrillation. On pressure immediately to the left of the second, third and fourth dorsal vertebrae and on torsion of the spine the "anginal" symptoms were exactly reproduced. Hyperesthesia to pinprick was present over the left hemithorax and the left breast was moderately tender to pressure. Radiographic examination of the spine revealed moderate hypertrophic changes with lipping and beaking along the anterior aspects of the bodies plus a slight scoliosis from the second to the fifth dorsal vertebrae.

Eight c.c. of 2 per cent novocain were injected into the paravertebral muscles to the left of the second, third and fourth dorsal vertebrae. The following day there was definite improvement with the "anginal" pain much less frequent and severe. By the second day the pain had completely disappeared and could no longer be reproduced by similar pressure or motion of the spine.

One month later she complained of pain in the lower back radiating anteriorly. There was exquisite tenderness with reproduction of the pain at two points over the left lumbo-sacral articulation. At each site 6 c.c. of 2 per cent novocain were injected and by the second day all pain had disappeared. There had been no recurrence of either pain 12 and 11 months respectively after injection.

Case 2. E. K., a 27 year old female with known rheumatic heart disease since the age of 15, complained of sharp intermittent pain under the left breast radiating posteriorly and accompanied by palpitation for the previous three months. Examination showed rheumatic heart disease with mitral insufficiency and stenosis and aortic insufficiency, auricular fibrillation and mild congestive failure. The blood pressure was 126 mm. Hg systolic and 50 mm. diastolic. The clinical status and laboratory data indicated that she had active rheumatic fever. The pain originally was believed due to the aortic insufficiency but nitroglycerine afforded no relief. Careful examination of the spine revealed that on pressure just to the left of the sixth dorsal vertebra the pain was reproduced and even exaggerated. There was diminished sensation to light touch and pinprick over the left chest anteriorly down to the sixth intercostal space and posteriorly down to the level of the fourth dorsal vertebra. Roentgenogram of the spine was normal.

At the point of tenderness 7 c.c. of 2 per cent novocain were injected into the deep paravertebral muscles with almost immediate disappearance of pain. For the subsequent nine months she was completely free from all pain and then she experienced a recurrence similar to the initial episode. At this time there was tenderness with reproduction of the complaint on pressure to the left of the first, second and fourth dorsal vertebrae. Six c.c. were injected into each of these areas and the pain was completely relieved within two hours. There had been no recurrence three months later.

RESULTS

All patients injected were relieved of their pain. Many were followed for over a year after injection with no recurrence. Several had a recurrence of symptoms from six to eight months later at which time the procedure was repeated and prompt relief was obtained. Frequently relief occurred within.

TABLE I

Paravertebral Muscles

Muscle	Extent and Possible Level of Injection	Nerve Supply
First Layer		
Trapezius	C7–D12	External branch of spinal accessory nerve Anterior primary divisions C(2), 3, 4
Latissimus Dorsi	D6–Sacrum	Thoracodorsal nerve (C5–8 of brachial plexus)
Second Layer		
Rhomboideus		
Major	C7, D1	Dorsal scapular nerve (chiefly anterior primary
Minor	D1–4(5)	division C5 of brachial plexus)
Serratus		
Posterior Superior	C7–D2(3)	Anterior primary divisions D1–4 = intercostal nerves
Serratus		
Posterior Inferior	D11–L2(3)	Posterior primary divisions C2–4 (C1, 5, 6)
Third Layer		
Sacrospinalis (Erector spinae)	L1–5	Posterior primary divisions L1–5
Iliocostalis		
Cervicis	C4–D7	Posterior primary divisions C8–L1
Dorsi	C7–D12	
Lumborum	D5(6)–L5	
Longissimus		
Capitis	C(5)6–D3(4)	Posterior primary divisions C1–L5
Cervicis	C2–D4(5, 6)	
Dorsi	D1–L5	
Spinalis		
Cervicis	C2–D2	Posterior primary divisions lower C
Dorsi	D2(3)–L2	D6–9
Semispinalis		Posterior primary divisions
Capitis	C3–D6	C1–4(5)
Cervicis	C2–D5	C3–6
Dorsi	C7–D10(12)	D3–6
Multifidus	C2–Sacrum	Posterior primary divisions C1–L3

10 minutes after injection but at times one to two hours elapsed before an effect was evident. In no case did a frank failure result. Three cases experienced only a moderate degree of relief following injection but on repetition of the procedure seven to 10 days later complete and permanent relief was obtained.

A not infrequent secondary effect was transient burning and superficial tenderness at the sites of injection apparently due to the muscle and subcutaneous infiltration. This always disappeared within eight to 12 hours. Thereafter, spontaneous pain was absent and pressure and manipulation of the spine at the site of injection could no longer precipitate it. The larger amount of novocain seems to have been no more effective than the lesser. In 56 injections given to 26 patients no complications occurred. At all times an attempt was made to eliminate the psychic effect of a new form of therapy in patients with chronic disease. The patients were never promised a therapeutic success and the element of suggestive therapy seems to have played little part in the end result. In several cases in which normal saline was injected instead of novocain, the pain was relieved for 12 to 24 hours but thereafter returned with its original intensity and distribution.

DISCUSSION

The mechanism of the radicular syndrome occurring in association with arthritic changes in the spine has been ascribed to an irritative process involving the nerve roots at their exit through the intervertebral foramina, either a proliferative bony compression,[3, 4, 5, 6] primary narrowing of the foramina,[7, 8] or soft tissue changes.[17] Inasmuch as the motor nerves also
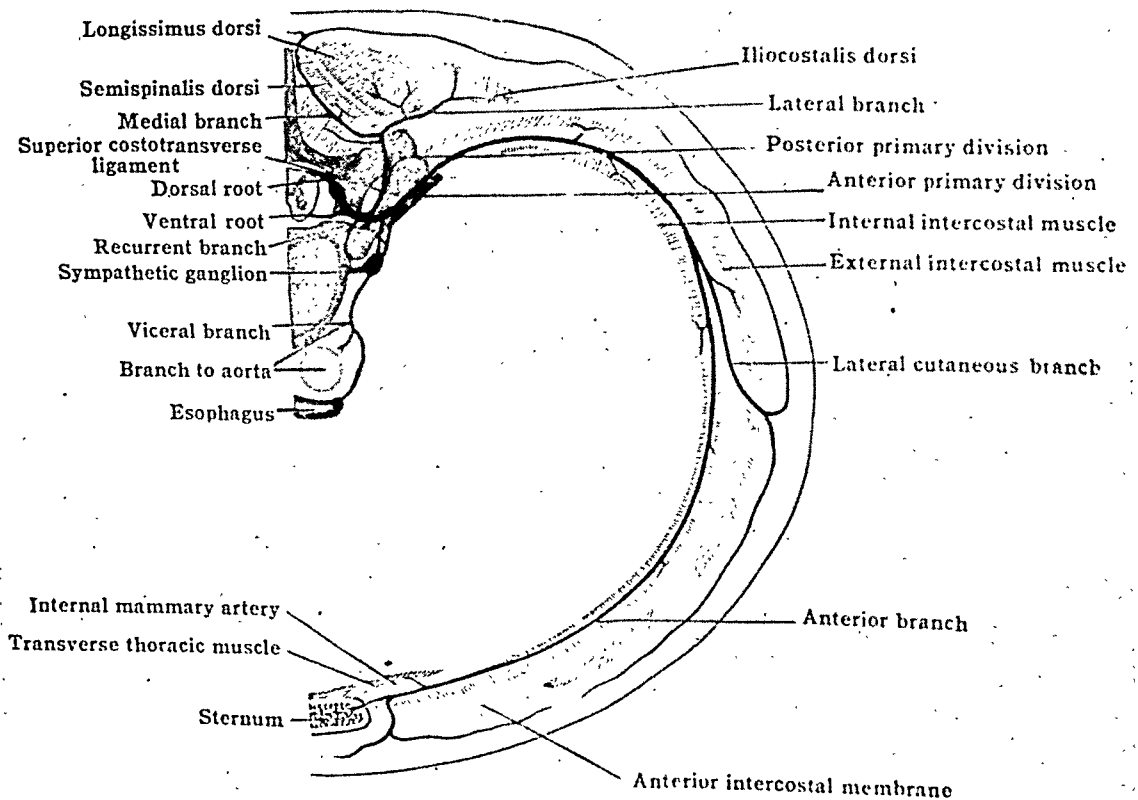
FIG. 1. Diagram of the distribution of a typical thoracic nerve.
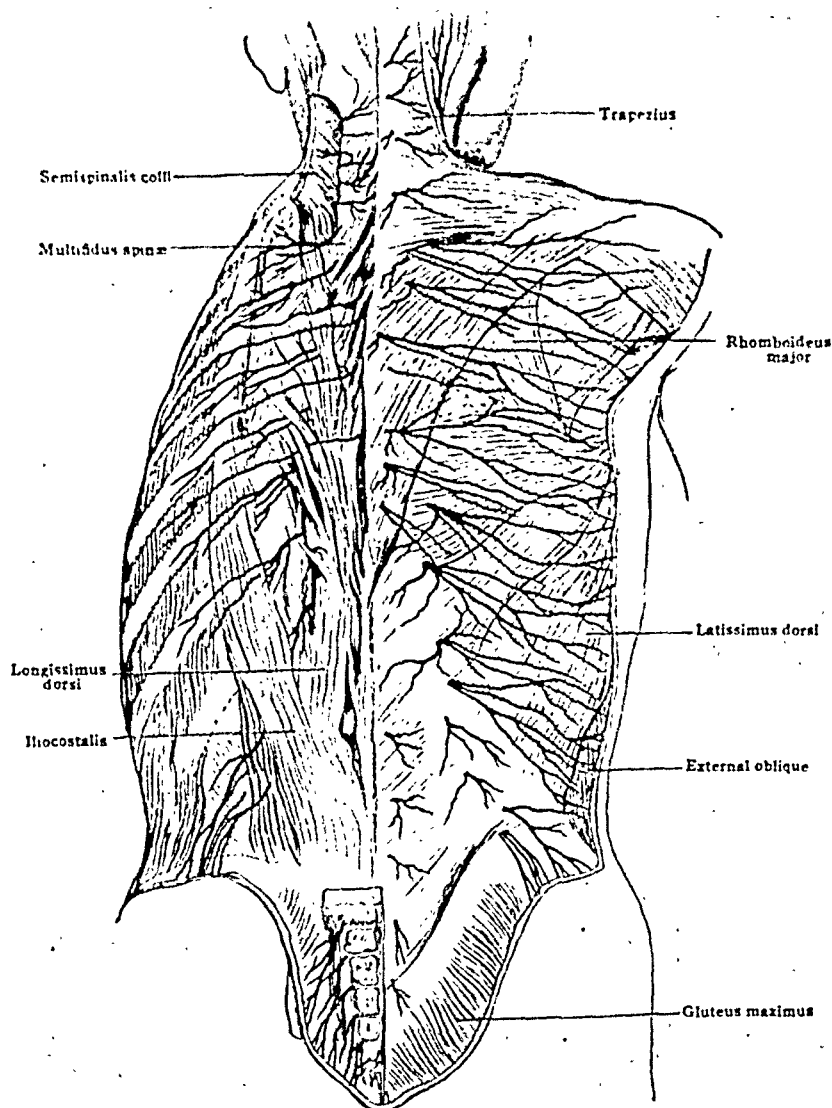
FIG. 2. Distribution of the posterior primary divisions of the spinal nerves (Henle).

possess protopathic sensations (Sherrington[18]), such an irritative process produces referral to the terminal portion of the nerve and, therefore, since these fibers run directly to the muscle bundles, muscular pain.

In this series of cases, however, as in Kellgren's observations, the widespread referred pain arises from the tender regions of the paravertebral muscles and interspinous ligaments. Since the somatic findings are always in close relation to arthritic spinal joints, it is reasonable to assume that the joint involvement is the primary cause and the muscular and ligamentous tenderness a secondary factor, either spasm or a localized "myositis" or "fibrositis." The widespread distribution of pain referred from the paraspinal muscles and its segmental relationship to the deeper visceral structures has been demonstrated by Kellgren. Simulated visceral pain occurs

because pain from the somatic structures is referred along the same path as that arising from a viscus (Lewis and Kellgren [19]).

The spinal nerves as they emerge from the intervertebral foramina divide into four branches: the anterior and posterior primary divisions, the small ramus communicans, and the smaller ramus meningeus. The posterior primary division after passing downward between the arches of the transverse processes divides (except the first cervical, fourth and fifth sacral, and coccygeal nerves) into medial and lateral branches, while the anterior primary divisions run laterally and ventrally as the direct continuations of the nerve trunks. As can be seen in figures 1 and 2, the paravertebral site of novocain infiltration includes the branches of the posterior ramus and more deeply the anterior ramus, as well as the muscles innervated by these nerves. A two-fold anesthetization is achieved in this manner so that, as a secondary effect, referral to the visceral structures is eliminated.

More difficult to explain, however, is the prolonged period of complete freedom from pain which follows the injection. Livingston [20] has ascribed the result of deep novocainization to the initial anesthetic action plus the expanding action of the solution itself. The fact that injection of normal saline is ineffective would seem to indicate that the novocain is a responsible factor. Gutstein-Good [21] and Moynahan [22] believe the pain of localized myalgias may be ascribed to the "vasomotor disequilibrium" theory of Leriche in which afferent impulses produced by local vasodilatation are responsible for the pain. The action of novocain is to block these impulses at their site of origin. Nevertheless, despite the absence of a satisfactory explanation of the underlying mechanism, empirically the method has proved extremely effective and, because of its simplicity and freedom from complications, merits continued clinical use.

SUMMARY

1. The effects of novocain injection into the deep paravertebral muscles in patients with simulated visceral pain due to spinal arthritis are reported.

2. Two groups of patients with simulated visceral pain were encountered —those with and those without visceral disease. In both groups results were uniformly good.

3. Although the effect is probably due to the dissolution of a vicious reflex cycle, a complete explanation of the prolonged therapeutic result cannot be offered.

BIBLIOGRAPHY

1. VON BECHTEREW, W.: Steifigkeit der Wirbelsäule und ihre Verkrümmung als besondere Erkrankungsform, Neurol. Centralbl., 1893, xii, 426.

2. GUNTHER, L., and KERR, W. J.: The radicular syndrome in hypertrophic osteoarthritis of the spine, Arch. Int. Med., 1929, xliii, 212.

3. GUNTHER, L., and SAMPSON, J. J.: The radicular syndrome in hypertrophic osteo-arthritis of the spine. Root pain and its differentiation from heart pain, Jr. Am. Med. Assoc., 1929, xciii, 514.

4. NACHLAS, I. W.: Pseudo-angina pectoris originating in the cervical spine, Jr. Am. Med. Assoc., 1934, ciii, 323.

5. HANFLIG, S. S.: Pain in the shoulder girdle, arm and precordium due to cervical arthritis, Jr. Am. Med. Assoc., 1936, cvi, 523.

6. KELLY, L. C.: Chronic hypertrophic osteoarthritis in the cervical spine with radiculitis. A report of forty cases with a review of the literature, together with some notes on effective methods of treatment. Parts I, II and III, New York State Jr. Med., 1942, xlii, 144, 246, 336.

7. TURNER, E. L., and OPPENHEIMER, A.: A common lesion of the cervical spine responsible for segmental neuritis, ANN. INT. MED., 1936, x, 427.

8. OPPENHEIMER, A., and TURNER, E. L.: Discogenetic disease of the cervical spine with segmental neuritis, Am. Jr. Roentgenol., 1937, xxxvii, 484.

9. BRAV, E. A., and SIGMOND, H.: The local and regional injection treatment of low back pain and sciatica, ANN. INT. MED., 1941, xv, 840.

10. KELLGREN, J. H.: A preliminary account of referred pains arising from muscle, Brit. Med. Jr., 1938, i, 325.

11. KELLGREN, J. H.: Observations on referred pain arising from muscle, Clin. Sci., 1938, iii, 175.

12. KELLGREN, J. H.: On the distribution of pain arising from deep somatic structures with charts of segmental pain areas, Clin. Sci., 1939, iv, 35.

13. KELLGREN, J. H.: Some painful joint conditions and their relation to osteoarthritis, Clin. Sci., 1939, iv, 193.

14. KELLGREN, J. H.: Somatic simulating visceral pain, Clin. Sci., 1940, iv, 303.

15. HARMAN, J. B., and YOUNG, R. H.: Muscle lesions simulating visceral disease, Lancet, 1940, i, 1111.

16. PARKER, H. L., and ADSON, A. W.: Compression of the spinal cord and its roots by hypertrophic osteoarthritis, Surg., Gynec., and Obst., 1925, xli, 1.

17. NATHAN, P. W.: The neurological condition associated with polyarthritis and spondylitis, Am. Jr. Med. Sci., 1916, clii, 667.

18. SHERRINGTON, C. S.: On the anatomical constitution of nerves of skeletal muscles; with remarks on recurrent fibers in the ventral spinal nerve-root, Jr. Physiol., 1894, xvii, 211.

19. LEWIS, T., and KELLGREN, J. H.: Observations relating to referred pain, viscero-motor reflexes and other associated phenomena, Clin. Sci., 1939, iv, 47.

20. LIVINGSTON, W. K.: Back disabilities due to strain of the multifidus muscle. Cases treated by novocain injection, West. Jr. Surg., Obst., and Gynec., 1941, xlix, 259.

21. GUTSTEIN-GOOD, M.: Idiopathic myalgia. Simulating visceral and other diseases, Lancet, 1940, i, 326.

22. MOYNAHAN, E. J.: Treatment of acute sprains by procaine infiltration (Leriche's method), Lancet, 1939, i, 672.

CALCAREOUS PANCREATITIS; REPORT OF THREE CASES WITH AUTOPSIES *

By Joseph G. Pasternack, M.D., *Staten Island, New York*

A casual survey of the literature on diseases of the pancreas discloses surprising periodic surges of interest in this organ, some of which have been epochal. As our familiarity with pancreatic disorders increases, functional tests and diagnostic aids evolve and existing ones are used more critically.

Roentgenologic exploration of the abdomen is not yet on the same plane of precision and importance as the chest plate. Our knowledge and interpretation of anomalous shadows in the abdomen consequently have not attained the same diagnostic reliability. However, the increasing frequency of reports on pancreatolithiasis in the last few years is an indication of a growing familiarity with this condition. The roentgen-ray has taken pancreatolithiasis out of the category of rare lesions, in years past reported as an accidental finding at operation or necropsy. Although a roentgenologist's experience may not permit an unequivocal diagnosis of pancreatolithiasis in some cases, correlation of the abdominal shadow with the clinical disease, when symptoms are present, is usually diagnostic.

The following cases, in all of which an advanced calcareous pancreatitis was found at autopsy, presented several of the more important clinical features of the disease.

CASE REPORTS

Case 1. A white seaman, aged 57, entered the Marine Hospital July 1, 1941, because of severe weakness, intractable diarrhea and weight loss of 40 pounds within 10 months. The symptoms began insidiously about 18 months earlier. For the past 12 months, the patient had an average of 10 to 12 bowel movements daily. There was no associated pain or colic; the stools were watery, copious, and offensive in odor. They were described as containing "mucus and pus."

In August 1937, this patient was treated here for "rheumatism and an attack of colic." Roentgenograms made then showed minor hypertrophic changes in the knees and ankles. An impacted stone was found in the right ureter and further studies disclosed a right pyonephrosis. The Kolmer and Kahn tests were negative. The urine contained no sugar, and the blood picture was not significantly altered.

In September 1937, a right nephrectomy with ureteral lithotomy and ureterectomy was done. Convalescence was extremely slow.

Urinalysis January 3, 1938, revealed sugar 2+. The fasting blood sugar on January 5 was 375 mg. per cent. On January 7, the dextrose tolerance curve was of the severe diabetic type and all urine specimens showed 4 + sugar. After the diabetes was controlled, convalescence was rapid and uneventful.

Roentgenograms on April 3, 1938, showed absence of the right kidney, calcification to the right of the bodies of the third, fourth and fifth lumbar vertebrae and a calculus in the vicinity of the left ureter near the urinary bladder. From April 1938,

until the onset of the present illness nearly two years later, the patient had been in fair health, worked hard, and made no effort to control his diabetes by diet or with insulin.

Physical examination at the present admission revealed pallor of the skin and mucous membranes, marked emaciation and muscular atrophy, and extreme dehydration. The tongue was beefy, red and furrowed. The patient was very weak and he had a hacking cough. The lungs were reported negative. The heart sounds were faint and there were numerous extrasystoles. Blood pressure was 75 mm. Hg systolic and 30 mm. diastolic. The abdomen was distended and tympanitic. There was no tenderness. The lower extremities showed marked pitting edema to just above the knees. Proctoscopic examination disclosed a minor degree of congestion of the rectal mucous membrane. The temperature was 37.6° C. on admission. The following day it was 39° C. and continued high until death.

The Kolmer and Kahn tests were negative. Urinalysis was negative. The red blood count was 4,000,000, hemoglobin 11 grams, and the leukocyte count and differential were within normal limits. The blood chemistry findings were: sugar 71, non-protein nitrogen 21 and chlorides 440 mg. per cent, respectively. The total protein was 5.7 grams/100 c.c. of serum and the A/G ratio was 1.03/1. Repeated stool examinations for parasites and cultures for pathogenic microörganisms were negative. A roentgenogram of the chest showed a dense shadow in the base of the right lung suggesting an infarct. Therapy of various types was of no avail and the patient died one week after admission.

Autopsy. The significant autopsy findings were as follows. The body was extremely emaciated and dehydrated. There was marked pitting edema of the scrotum and of the lower extremities from the mid-thighs down. The peritoneal surfaces were dry and lustreless. The urinary bladder was entirely empty. The loops of the small intestine were greatly distended with gas. The pericardial sac contained about 5 c.c. of normal fluid.

Lungs. The left lung weighed 1050 grams. The upper lobe was water-logged and the lower lobe showed extensive pneumonic consolidation. The right lung weighed 1900 grams. The medial side and base were inseparably fused with the paravertebral tissues. After removing the lung, a partially encapsulated abscess was found along the spine which apparently was part of the lesion in the lower lobe of the lung. On section, the parenchyma of the upper lobe showed extensive pneumonic consolidation. The lower lobe presented a large abscess marginated by smaller satellites. The bordering parenchyma was gangrenous.

Liver. The liver weighed 1700 grams. It was pale yellow in color and on section the parenchyma was of ordinary consistency. The gall-bladder was greatly distended with colorless watery fluid (white bile). The biliary ducts were patent and showed no lesions. The ampulla of Vater was prominent and the orifice contained granules of calcareous material, some of which were expelled after prolonged and vigorous pressure upon the gall-bladder.

Pancreas. Weight 400 grams. Its normal configuration was entirely lost. Handling imparted the impression of a sac filled with crunching and grating pebbles and stones. Satisfactory dissection of the organ could not be accomplished because it was entirely converted into a calcareous mass. Piece-meal dissection disclosed cystic spaces filled with multiple small and large hard, grayish, angular and sharp calculi. Deposits of hard gravel were present throughout the organ. Some of the cysts had a smooth wall and communicated with each other freely, apparently the remains of ducts. Pancreatic parenchyma was not demonstrable.

Aorta. The abdominal segment from the bifurcation upward presented a fusiform aneurysm 7 cm. in its greatest diameter and 10 cm. in length. The wall of the aneurysm was completely calcified. It was inseparably fused with and completely

compressed the inferior vena cava. The atherocalcareous process involved the common iliac arteries in their entirety so that they were pipestem in character.

Gastrointestinal Tract. The mucous membrane of the stomach was thin, ironed out and very pale. The wall of the intestines was thin and diaphanous. The mucous membrane throughout the intestinal tract showed advanced atrophy. There were no foci of ulceration or inflammation.

Histologic Examination. Histologic sections of the aortic aneurysm showed advanced diffuse atheromatous degeneration and calcification of the entire wall with little hyalinized scar remaining. The lungs showed confluent bronchopneumonia. The abscess in the left pulmonary base consisted of purulent necrotic material bordered by hemorrhagic and necrotic suppurating parenchyma. The liver showed extensive, advanced fatty metamorphosis of the hepatic cells.

The pancreatic parenchyma was practically entirely replaced by dense fibrous and hyalinized connective tissue. Rarely small groups of acini, showing more or less atrophy, were seen. Occasional islets of Langerhans remained. Some showed atrophic changes and others interstitial fibrosis. Cystic spaces of various sizes, having a dense fibrous wall, prevailed. In their wall isolated, atrophied and deformed acini were occasionally present. Segments of the wall were often incrusted with calcium. Here and there systems of dilated, distorted, ramifying ducts occurred. They had no lining or one of simple cylindrical or cubical epithelium. In the smaller ducts the epithelium showed short stretches of diffuse squamous metaplasia and hyperkeratosis. Some ducts were filled with desquamated cornified epithelium. In some it was mixed with amorphous calcified debris. Deposits of calcifying amorphous debris were present here and there throughout the fibrous stroma. In areas the fibrous tissue was vascularized and dense focal infiltrations of lymphocytes were present. The blood vessels of the pancreas showed diffuse fibrosis of their wall and the larger nerves showed more or less fibrosis of their sheath. Several large arteries showed more or less calcification of their wall.

Case 2. On September 17, 1941, a white male, aged 46, a sanitary inspector, was hospitalized for the treatment of pulmonary tuberculosis and diabetes mellitus. The patient had been under treatment for severe diabetes for two years. For the five months past, he had not followed his diet and used no insulin. During this period, he lost 40 pounds and became very weak. In April 1941, he had an attack of pleurisy. Roentgenograms disclosed a tuberculous lesion in the left lung. His health was growing progressively worse.

Physical examination revealed a pale, sick, febrile, coughing, emaciated patient. Laboratory studies disclosed a severe diabetes mellitus. Roentgenograms showed active tuberculous lesions in both lungs. The sputum contained acid-fast bacilli. Although the diabetes was completely controlled and the patient was on a rigid régime for his tuberculosis, the disease progressed rapidly and he died three and one-half months after admission. There were no abdominal symptoms at any time and he had no diarrhea.

Autopsy. At autopsy both lungs showed chronic ulcerative tuberculous lesions in the apices and tuberculous bronchopneumonia throughout the remainder of the parenchyma.

Pancreas. Weight 180 grams. It was hard, granular and gritty. Sectioning disclosed the ducts to be dilated and filled with sharp, hard, angular, grayish-white calculi, some of which had cut their way into the parenchyma of the organ. In areas the main duct and its branches were cystic and filled with colorless fluid in which sandy material was present. Here and there throughout the organ chalky deposits and embedded collections of gravel were present. In areas remains of sclerosed parenchyma were detectable.

Histologic Examination. The histologic sections showed marked dilatation and

deformity of the ducts. Their wall was thickly fibrosed. Some were lined only by fibrous tissue and others showed focal calcification. The parenchyma was largely replaced by dense, acellular fibrous tissue. Here and their islands of acini ensnared in scar tissue remained. Very few islets of Langerhans were seen, some associated with acini and some solitary in the fibrous stroma. Deposits of amorphous calcified material were present apart from duct structures and these were often bordered by stray acini. In areas dense infiltrations of lymphocytes were encountered.

Case 3. A white male, aged 56, a known diabetic for more than 20 years, was hospitalized because of nervousness and mental confusion.

A history elicited from the patient's two sisters, both nurses, disclosed the following. The patient had had nausea, vomiting and severe diarrhea for the past five months. These attacks were occasionally associated with colic and pain over the stomach. The patient had no appetite and in a few months had become markedly emaciated. Despite repeated hospitalization and nearly constant medical attention the patient's abdominal condition was not diagnosed and treatment did not help. One year previously the patient had a periproctic abscess which was incised and drained, and healed. Now he had a painful lump in the same place.

Physical examination revealed a dull, apathetic, pale, emaciated patient. The oral mucous membrane was pale. There was moderate pitting edema of the lower extremities up to the mid-thighs; also the prepuce and lower eyelids were edematous. The temperature was 37.5° C. A large periproctic abscess which extended into the right ischiorectal fossa was present.

The urine contained a trace of albumin and no sugar. The blood chemistry showed sugar 128, non-protein nitrogen 29 and cholesterol 143 mg. per cent, respectively. The total protein was 4.2 grams/100 c.c. of serum.

Four days after admission the periproctic abscess was incised and drained. The abscess pointed to the right of the anus. It extended around the dorsal and ventral sides of the rectum and for some distance into the right ischiorectal space. Six days after operation another abscess appeared at the left side of the anus. It was opened and drained, and found to be an extension of the first lesion. Although the patient's diabetes was apparently under control, he lapsed into a state of stupor. Three days after the second operation the tissues around the anus and over the sacrum became black, fluctuant and crepitant. Cultures disclosed *Cl. welchii* and *B. coli.* The infection spread rapidly and the patient died two days after the onset of gangrene.

Autopsy. At autopsy the skin over the greater part of the back, the nates, around the anus, over the loins and over the posterior aspect of the left thigh was black, wet, gangrenous and emphysematous. Incisions into the gangrenous areas disclosed extensive hemorrhagic necrosis, copious extravasation of blood-tinged fluid and escape of gas bubbles from the fluid. Exploration of the periproctic tissue disclosed advanced suppuration and liquefaction of the perianal and perirectal tissues. Other significant findings were as follows.

Pancreas. Weight 250 grams. The specimen consisted of a deformed, sclerosed sac of stones. Piece-meal dissection disclosed several large sharp calculi in the head and numerous smaller ones throughout the duct system. Deposits of gravel were present throughout the sclerosed parenchyma. The ducts were dilated, cystic and sacculated. Whitish turbid fluid was present in some parts of the duct system.

Histologic Examination. Histologic examination disclosed a diffuse productive pancreatitis with practically complete replacement and destruction of the parenchyma. Large areas of liposis were present.

The lungs showed widespread tuberculous bronchopneumonia. The liver showed irregular fatty metamorphosis. The fundus of the gall-bladder was thickened. The bile ducts were moderately dilated, but showed no other changes. Subchronic dif-

fuse glomerulonephritis was present. There was advanced, generalized atherosclerosis. The abdominal aorta and common iliac arteries showed marked atheromatous ulceration and calcification of their wall.

DISCUSSION

Etiology. The cause of stones in the ducts and calcareous changes in the parenchyma of the pancreas is not definitely known. In many cases the lesion has been associated with chronic disease of the biliary tract and with cholelithiasis. Infection by way of the ducts, regurgitation from the biliary tract, and stasis of pancreatic secretion are probably important contributing causes to the formation of duct stones. Squamous metaplasia of the duct epithelium is not infrequently observed. Desquamated, cornified epithelium may serve as a nidus for calcification in the ducts. Etiologic significance is also attributed to alcoholism in that some patients were chronic alcoholics. In a few cases cirrhosis of the liver, and fatty metamorphosis have been found. The fatty change in the liver is believed to be due to a disturbance in the secretion of a pancreatic hormone, lipocaic, which regulates the deposition of fat in the hepatic cells.

Calcification of the parenchyma is probably also a sequel of infection, inflammation and necrosis. Infection may occur by contiguity from adjacent structures, through the pancreatic ducts, or through the blood stream, but it probably occurs most frequently by way of the lymphatics. Free communication is present between the lymphatics of the pancreas and those of the biliary tract, stomach and duodenum.

A recent study [1] presents interesting observations that may explain the pathogenesis of chronic calcareous pancreatitis. In acute pancreatic necrosis, the fat necrosis has been shown to be due to the splitting of neutral fat into fatty acids and glycerin by the action of lipase that has escaped into the tissues from the pancreatic juice. The glycerin is absorbed and the fatty acids combine with calcium to form insoluble soaps. These authors demonstrated large quantities of calcium in acute pancreatic lesions, and they found a moderate fall in the serum calcium of patients with acute pancreatic necrosis, between the third and the eleventh day of the disease. Three instances of tetany associated with acute pancreatic necrosis have been reported.

In patients with pancreatolithiasis there is frequently a history of obscure attacks of abdominal pain and of episodes of vague gastrointestinal disturbances of variable severity, as in case 3 of the present series. These may well represent subclinical or abortive attacks of acute pancreatic necrosis. Once formed, a focus or foci of calcification continue to grow by the further addition of calcium salts. Secondary changes due to mechanical irritation and inflammation probably favor the progress and dissemination of the lesion to involve more or less of the pancreas. The mechanism of the influence of the parathyroids upon calcification is poorly understood, but an upset in the calcium balance may be a factor.

Calcification of the parenchyma may occur without associated concretions in the ducts, or gravel and calculi may be found only in the ducts. In advanced lesions the calcareous deposits occur throughout the pancreas and the most careful dissection and histologic studies cannot disclose which deposit was first.

The time required for stones in the ducts to form or for calcareous pancreatitis to develop is indefinite and highly variable. Pancreatic concretions are composed chiefly of calcium carbonate and calcium phosphate and, therefore, are likely to show in roentgenograms. In case 1 of the present series, roentgenograms of the abdomen made in 1937 and in 1938 showed no shadows in the region of the pancreas, yet two and one half years later ad-

FIG. 1. Pancreas: roentgenogram of autopsy specimen showing extensive lithiasis (case 1).

vanced pancreatolithiasis (figure 1) was found at autopsy. Others have reported stone formation after shorter intervals and some after much longer periods of observation.

Pathologic Anatomy. The pathologic anatomy of calcareous pancreatitis affords the explanation for the pathologic consequences of the disease.

The concretions may consist of sandy or gravel deposits free in the ducts or incrusted over their wall. The ducts may be pipestem in character. Calculi as large as walnuts have been reported. Usually duct stones are multiple, or very numerous. They are of a grayish or brownish-gray color, hard, rough and angular, often sharp. They may be stag-horn or branched like coral. Sometimes they are facetted. The larger stones are usually found

in the head near the duodenal orifice of the pancreatic ducts, but they may be in any part of the gland. Gravel and stones may be deposited throughout the parenchyma of the pancreas. Usually parenchymal calcification consists of crumbly chalky gravel in large or small collections. Frequently the con- cretions are mixed with yellowish or chocolate colored organic matter.

The ducts are dilated, elongated and deformed. Not infrequently they show thickening and sclerosis of their wall and segmental cystic changes, and occasionally true retention cysts are formed.

The consequences of calculi and calcareous deposits are atrophy and progressive fibrosis with more or less destruction of the parenchyma of the

FIG. 2. Roentgenogram of calculus in Vater's papilla (case 1).

gland. The fibrosis is first interlobular and finally interstitial. The acinar tissue is affected first and most markedly. The islets of Langerhans are not significantly involved until the disease is far advanced. Only parts or all of the organ may be involved. Frequently it is converted into a sclerosed stony mass or into a sac of rocks. Suppuration and abscess formation may super- vene in any stage of the disease. Stones may erode into the abdominal cavity or fragments may slip into the papilla of Vater as in case 1 of the present series (figure 2).

As a result of obstruction of the ducts or the destruction of the acinar tissue disturbances due to a deficiency of the pancreatic enzymes in the in- testine may be conspicuous. Diabetes occurs when enough of the Langer-

Fig. 3. Roentgenogram of calcified aneurysm of aorta (case 1).

Fig. 4. Pancreas: roentgenogram of autopsy specimen showing extensive calcareous deposition (case 2).

hans islets are destroyed. However, even with advanced lesions there may be no symptoms, probably because the secretions of the stomach and intestines are capable of functioning vicariously.

Clinical Features. The clinical manifestations of calcareous pancreatitis are usually both vague and variable, and without roentgenograms a medical diagnosis of pancreatolithiasis could not be established. The more characteristic symptoms depend chiefly on the size, location and mobility of the stones in the main ducts and the secondary changes in or about the pancreas. Pancreatic colic is usually in no way distinguishable from biliary colic and was present in about two-thirds of the reported cases. The colic of pancreatic stone may be associated, however, with left sided extension and such pain may be further projected into the left costovertebral angle. The presence or absence of jaundice is not very significant, as jaundice is often lacking in cholelithiasis and is occasionally present in pancreatolithiasis. In the latter it may be due to compression of the common bile duct, or to obstruction of the papilla of Vater (figure 2).

It has been observed that episodes of acute pancreatic necrosis may occur with pancreatolithiasis. The symptoms are those of acute pancreatitis and should not be confused with pancreatic colic.

Various reflex digestive disturbances such as pylorospasm or gastrospasm, gastric hypersecretion, episodes of nausea and vomiting not associated with pain or colic, intestinal hypo- or hypermotility and other bizarre reactions which might be regarded as functional have been observed.[2]

Signs and symptoms of pancreatic insufficiency are present in about half of all cases of calcareous pancreatitis. Frequent bulky pale stools, marked inanition and extreme asthenia are the most characteristic clinical manifestations. Large amounts of fat and numerous undigested muscle fibers are present in the stool. Correlation of the signs and symptoms with visual examination of a 24 hour specimen of stool usually suffice for a presumptive clinical diagnosis, to be verified by roentgen examination, without which a diagnosis of pancreatolithiasis is practically impossible.

Physical examination may disclose tenderness in the epigastrium and an indefinable mass in the region of the pancreas, but usually it is not helpful.

It is significant that extensive damage to acinar tissue may be present without concomitant islet damage of sufficient severity to produce diabetes. However, latent and active diabetes mellitus is present in about 50 per cent of all cases of pancreatolithiasis. Often there is no evidence of associated pancreatic achylia. Obviously there is considerable variation in the amount of acinar and islet tissue destroyed, but also the magnitude of the disturbance in digestion and absorption that occurs when pancreatic insufficiency is present varies in different individuals. Diabetes may antedate the lithiasis by years, appear concomitantly, or develop after the lesion is far advanced. In case 1 of the present series diabetes was present at least two years before calcareous pancreatitis developed. Case 2 was a diabetic for two years

before he developed tuberculosis and died. Case 3 was a diabetic for more than 20 years before symptoms of pancreatic achylia ensued.

The statement that pancreatic duct stones are frequently found in diabetics has no support in the postmortem findings of large diabetic groups.[3] It is noteworthy that cholecystic disease and cholelithiasis occur in 25 to 30 per cent of diabetics and yet pancreatolithiasis is rarely found. These facts do not substantiate the statements that chronic biliary tract disease is an important etiologic factor and that pancreatolithiasis is frequently associated with cholelithiasis.

The clinical diagnosis of calcareous pancreatitis depends upon the roentgenographic demonstration of calcification in the pancreatic region. Pancreatic stones are usually sufficiently radiopaque to cast a shadow. However, it has been pointed out that they are best visualized in an oblique roentgenogram, and may often be missed in ordinary films of the kidneys, ureters and bladder or in cholecystograms. When the clinical disease is not suspected, shadows of stones in the pancreatic region may go unheeded or without proper interpretation.

Without special laboratory procedures, occasionally pancreatogenous diarrhea may be difficult to differentiate from sprue, idiopathic steatorrhea, celiac disease, exclusion of bile from the intestine, certain cases of enteritis and colitis, and other conditions characterized by frequent bulky stools. The diagnosis can be established by demonstrating (a) an absence or deficiency of pancreatic enzyme in duodenal drainage and (b) an excess of both fat and nitrogen in the stool. There is usually clinical improvement with oral pancreatic enzyme therapy.

Many of the reported cases of calcareous pancreatitis either had or died of pulmonary complications. In the present series, two patients died of tuberculous bronchopneumonia and one of pulmonary abscess and gangrene. It has been observed that patients with prolonged pancreatic insufficiency are predisposed to pulmonary tuberculosis, suppuration and gangrene. Obsolete or other tuberculous lesions have rarely been demonstrated in the pancreas.

Treatment. When the symptoms are principally those of pancreatic achylia oral pancreatic enzyme therapy is highly effective.[4] The response is characterized by a decrease in the frequency and bulk of the stools, associated with gains in weight and increased strength.

Cases not too far advanced are amenable to surgical treatment. A number of surgical successes have been reported.

SUMMARY

Three cases of calcareous pancreatitis with autopsy findings are reported. The pathogenesis of the lesion, the pathologic physiology and the diagnostic features of the disease are presented.

BIBLIOGRAPHY

1. EDMONDSON, HUGH A., and FIELDS, IRVING, A.: Relation of calcium and lipids to acute pancreatic necrosis, Arch. Int. Med., 1942, lxix, 177–190.
2. SNELL, ALBERT M., and COMFORT, MANDRED W.: The incidence and diagnosis of pancreatic lithiasis, Am. Jr. Digest. Dis., 1941, viii, 237–243.
3. DRY, THOMAS J., and TESSMER, CARL F.: Postmortem findings in cases of diabetes, Minnesota Med., 1941, xxiv, 96–105.
4. BEAZELL, J. M., SCHMIDT, ROBERT C., and IVY, A. C.: The diagnosis and treatment of achylia pancreatica, Jr. Am. Med. Assoc., 1941, cxvi, 2735–2739.

ALLERGIC REACTIONS TO LIVER EXTRACT *

By Robert E. Kaufman, Captain, Medical Corps, U. S. Army,
Laurence Farmer, M.D., and Carl Reich, M.D.,
New York, N. Y.

Reactions to liver extract, usually clearly of an allergic nature, have been reported by numerous authors [1-35] since 1931. These 35 articles record a total of only 50 patients experiencing reactions from liver extract by injection. The condition is by no means so rare, however, as the above number would indicate. In this article we are reporting 11 additional cases, four seen personally and seven whose detailed histories were given us by two of our colleagues (table 1). Dr. Guy Clark of the Lederle Laboratories wrote us that "over a period of several years we have received approximately 30 reports of rather serious allergic-like reactions following the parenteral administration of liver extract." [36] The medical director of another large laboratory has also told us of "several" such cases reported to him. [37] Some of the cases in the files of these companies have probably been published in various American journals, and may be included, therefore, in the total of 50 cases in the literature. Most internists and general practitioners have undoubtedly seen similar cases; and it seems certain that the physicians in every large hematology clinic have witnessed such reactions.

There have been a few reports [18, 38, 39, 40, 41, 42] of allergic reactions from the ingestion of liver, either raw or cooked, or of liver extract. The total number of cases described in these articles is only seven or eight. Thus, it seems that reactions are much less common when liver is taken orally than parenterally. This would appear logical when it is remembered that the reaction-producing substance in whole liver is markedly concentrated when an extract suitable for injection is prepared.

From an analysis of the cases of reactions from injections of liver extract,[1-37, authors] it appears that the make of extract has little or no relation to the incidence of such reactions. Reactions have occurred after injections of all of the following: the original, moderately crude extract used by Murphy in Boston; the most concentrated commercial product, Reticulogen; various other Lilly extracts; several Lederle varieties; Parke, Davis' extract; Cheplin's extract; and the European preparations: Campolon, Exhepar, Eparina, Examen, Pernaemon, Hepatrat, and Heptomin. Many patients experiencing reactions from one brand also had reactions from other makes. The amount of extract injected may be the determining factor in some instances, but not in all. One patient [32] had a reaction after the administration of but 0.2 c.c. Campolon, a relatively dilute extract. Some patients have experienced generalized allergic manifestations after as little as 0.1 c.c. in-

tracutaneously,[7, 9, 10] and one had a severe local reaction after a test dose with the minute amount of 0.1 c.c. of a 1 : 1,000 dilution intracutaneously.[10] One of our patients (case 2) usually had a reaction after 1.0 c.c. Reticulogen, whereas 0.5 c.c. was usually tolerated.

A remarkable and inexplicable fact is that most patients have their first reaction after numerous injections and then never have another, even though receiving the same brand and the same quantity. This may be due, in some

TABLE I

Allergic Reactions to Liver Extract Injections

	Patient 1	Patient 2	Patient 3	Patient 4
Age	57	48	55	52
Sex	M	F	F	M
Other allergic manifestations	None	None	None	None
Make and amount of extract given	Lederle's ext. 3 c.c.; Reticulogen 1 c.c.	Lederle's ext. 3 c.c.; Reticulogen 0.5 c.c.–1.0 c.c.	Lederle's ext. 3 c.c.; Reticulogen 2 c.c.	Lilly's conc. ext. 3 c.c.
No. of injection when reaction occurred	Reaction many times; after many injections	Reaction many times; after many inj.	Reaction once; after many inj.	Reaction after 1, 2, 5 inj.
Clinical manifestations	Congestion and itching of conjunctivae and sclerae; edema, redness, itching of hands; occasional tightness in chest with cough. (Similar type reaction with both makes ext.)	Epigastric and sub-xiphoid pain with nausea and occ. vomiting— similar to pt's spontaneous anginal attacks. (Similar type reaction with both makes extract.)	Pounding and pain in head; flushed face; watering of eyes; taste of liver ext. (Reaction once only: after an injection of Lederle's ext. 3 c.c.)	First: urticaria; Second: scarlatiniform eruption; Third reaction: erythema, itching, and edema of arm.
Time from injection to onset of reaction	10–20 minutes	3–10 hours	Less than 1 minute	1.10 minutes 2.5 minutes 3.12 hours
Time reaction lasted	15–45 minutes	½–4 hours	5 minutes	1. 36 hours 2. Few hours 3. 4 days
Treatment given	Adrenalin with relief	Nitroglycerine with relief	None	Ephedrine; calamine lotion
Subsequent injections	Yes	Yes	Yes	Not after third reaction
If so, what reactions	Gradually desensitized: w. Reticulogen	Gradually desensitized: w. Reticulogen	None	—
Skin tests with liver extract	Yes (see chart)	Yes (see chart)	Yes (see chart)	No

TABLE I—(*Continued*)

	Patient 5	Patient 6	Patient 7	Patient 8
Age	54	68	37	32
Sex	F	F	F	M
Other allergic manifestations	None	None	?	None
Make and amount of extract given	Lederle's ext. ? c.c.; Reticulogen: ? c.c.; Cheplin's ext. 5 c.c.	Cheplin's conc. ext. 2 c.c.	Reticulogen 0.5 c.c.	Reticulogen 0.5 c.c.
No. of injection when reaction occurred	Lederle's: ? inj.; Reticulogen: after 7 inj.; Cheplin after 50 inj.	After 7th. inj.	After 1st. inj.	After 2nd. inj.
Clinical manifestations	Angioneurotic edema of lips and eyelids; general urticaria. (Similar type reaction after all 3 makes of extract.)	Urticaria of arms and wrists	Urticaria of face and arms	Pruritic, erythematous, maculopapular eruption—generalized.
Time from injection to onset of reaction	15 minutes	30 minutes	1 hour	2 days
Time reaction lasted	2 hours	30 minutes	Few minutes	12 days
Treatment given	Ephedrine	None	None	?
Subsequent injections	Yes	Yes	No	No
If so, what reactions	None	None	—	—
Skin tests with liver extract	No	No	No	No

instances, to inadvertent intravenous injection. Very rarely a reaction occurs after the first injection (case 4, this paper), but much more commonly the initial reaction is noted after the product had been well tolerated for weeks, months, or even years,[18, 30, 36, 43, authors] and especially after a long interval since the previous injection. This is apparently characteristic of allergic reactions from biologic products. As Criep [43] has well expressed the situation: "There is no prediction when an allergic reaction to a biological product may develop or when it will fail to develop. A patient may show a reaction to an injection today, none for the next two or three injections, and then another reaction later. These patients do not react with the same unfailing constancy following exposure to the respective allergens

TABLE I—(*Continued*)

	Patient 9	Patient 10	Patient 11
Age	68	40	71
Sex	F	F	F
Other allergic manifestations	None	None	None
Make and amount of extract given	Reticulogen 1 c.c.	Reticulogen 1 c.c.	Reticulogen 1 c.c.
No. of injection when reaction occurred	After 10th inj.	After 8th inj.	After 20th inj.
Clinical manifestations	Swelling and itching of palms	Itching of entire body	Itching of entire body
Time from injection to onset of reaction	1 hour	30 minutes	1 hour
Time reaction lasted	2 hours	3 hours	6 hours
Treatment given	Local	Local	None
Subsequent injections	Yes	No	No
If so, what reactions	None	—	—
Skin tests with liver extract	No	No	No

that atopic persons, such as hay fever patients, show when exposed to pollen." Sensitivity to liver extract may persist for long periods of time, even up to eight years in one instance.[27]

The average age of the 41 patients exhibiting reactions, whose ages were stated in the published reports, was 50 years. The youngest, with one exception—a 10-month-old infant [14] who was omitted from the average—was 24; the oldest was 73. Of the 47 patients whose sex was recorded, 33 or 70 per cent were females. Of the 61 cases of reactions to liver extract (including our 11) reported in the literature, only six are definitely stated to be allergic patients; 13 are definitely stated to show no other allergic manifestations, and in the remainder no statement is made.

Clinical. The clinical manifestations of reactions from liver extract are very varied. The commonest is urticaria, either alone or in association with other allergic symptoms. Local reactions, with pain, edema, erythema, and itching, are probably more common than the number of such cases in the literature would indicate, since frequently such relatively slight reactions, compared with the more dramatic occurrences, have probably not been considered important enough to warrant publication. Angioneurotic edema has been reported in many patients, as has asthma. A typical, severe, generalized reaction was reported by Grün.[10] His patient, a 56-year-old female with primary anemia, had been receiving injections of Exhepar without incident for some time. A few minutes after an intramuscular injection

weakness, a rapid and weak pulse, vomiting, dyspnea, urticaria, and a marked fall in blood pressure were noted; recovery occurred after administration of adrenalin.   Diena[7] reported the case of a 73-year-old female who developed abdominal pain, nausea, vomiting, urticaria, sweating, tachycardia, and dyspnea a few minutes after the third injection of Campolon.   Another patient, a 39-year-old male, noted warmth and flushing of the face and neck after the fifteenth liver extract injection; generalized urticaria, followed the next day by generalized glandular enlargement, appeared after the sixteenth injection; and perspiration, asthma, tachycardia, and urinary incontinence followed the seventeenth injection.[4]   Hafström's patient[17] developed severe anaphylactic shock with edema and urticaria, collapse, loss of sphincter control, and cyanosis.   Segerdahl's patient[22] had flushing of the face, injection of the conjunctivae, pain in the back, oppression in the chest, and asthma. Roovers[25] reported one patient who had severe asthma with pulmonary edema, and a second who had pain locally, edema of the face and tongue, and tingling in the fingers.   Kuipers[24] described a patient who showed angioneurotic edema, an exanthem, generalized itching, and pain in the joints. An interesting reaction was reported by Chaudhuri[6]: shortly after the first injection of 2 c.c. Campolon into the right gluteus muscle, there appeared itching, pain and swelling over the left deltoid muscle, followed by generalized itching and urticaria.   Held and Goldbloom[5] report a remarkable combination: on several occasions their patient developed renal colic, urticaria, erythema nodosum, pruritus, and pain in the right knee joint after the intramuscular injection of liver extract.   Engel[16] had a patient who experienced a tremendous local reaction with edema and redness, nausea, diarrhea, and weakness after a test dose of 0.1 c.c. intracutaneously.   Gardner[39] described the unusual occurrence of weakness, dizziness, palpitation, and uterine bleeding on several occasions after various oral preparations of liver extract. If we mention the case[17] with severe nasal and ocular discharges and substernal oppression, almost the whole gamut of allergic manifestations will have been described.   No fatalities have been reported.

Tests.   Intracutaneous testing with various brands of liver extract has been reported by many investigators.[2, 7, 8, 9, 10, 11, 13, 14, 16, 20, 29, 33, 34, authors] The total number of patients who had allergic reactions from liver extract and who were subsequently tested intracutaneously is 26, of whom 24 showed positive skin tests.   The passive transfer technic was employed additionally by several authors.[2, 7, 9, 10, 11, 14, 16, 20, 29]   Of 11 patients thus studied, eight showed positive tests.   Several investigators used 0.1 c.c. of the extract, which is too large an amount for most intracutaneous tests, as it will frequently give false positive reactions.   We feel that one should employ 0.02– 0.03 c.c. with a maximum of 0.05 c.c.   The interpretation of the results of the intracutaneous tests with liver extract is difficult.   Allin and Meyer,[44] using 0.05 c.c. undiluted liver extract, found that 14 of 15 normal individuals developed wheals, and therefore "arbitrarily decided that the appearance of wheals per se was not considered representative of a positive reaction, but

that any reaction showing pseudopods should be taken as positive." We found, from a study of some normal individuals, that with the diluted extracts in amounts even as small as 0.02 c.c., a wheal up to 12 to 15 mm. in diameter is normal. Therefore, the reaction was not considered positive unless the wheal was over 15 mm. in diameter or unless pseudopods were present; and the latter were never noted unless the wheal was over 15 mm. in diameter. As examples of our interpretation, a wheal 12 by 15 mm. with no pseudopods is negative; a wheal 16 by 20 mm. with no pseudopods is one plus; a wheal 22 by 25 mm. or 20 by 30 mm. with or without pseudopods is two or three plus; and a wheal 22 by 40 mm. with pseudopods is four plus.

TABLE II

Skin tests

Patient 1

Allergen	Scratch	Puncture	Intradermal	Intradermal	Intradermal
			undiluted 0.02 c.c.	diluted 1 : 10 0.02 c.c.	diluted 1 : 100 0.05 c.c.
Reticulogen............	+	+	++++	++	+
Lederle's ext..........	neg.	neg.	+++	+	neg.
Lilly's ext.............	neg.	neg.	+	+	neg.
Pork muscle...........	neg.	neg.	neg.	N.D.	N.D.
Beef muscle...........	neg.	neg.	neg.	N.D.	N.D.
House dust............	neg.	neg.	neg.	N.D.	N.D.
Ragweed..............	neg.	neg.	·N.D.	N.D.	N.D.

Patient 2

Allergen	Scratch	Puncture	Intradermal	Intradermal	Intradermal
Reticulogen............	neg.	neg.	+	+	+
Lederle's ext..........	neg.	neg.	neg.	neg.	N.D.
Lilly's ext.............	neg.	neg.	neg.	neg.	N.D.
Pork muscle...........	neg.	neg.	neg.	N.D.	N.D.
Beef muscle..........	neg.	neg.	neg.	N.D.	N.D.
House dust............	neg.	neg.	neg.	N.D.	N.D.
Ragweed..............	neg.	neg.	N.D.	N.D.	N.D.

Patient 3

Allergen	Scratch	Puncture	Intradermal	Intradermal	Intradermal
Reticulogen............	neg.	+	+++	neg.	N.D.
Lederle's ext..........	neg.	neg.	neg.	neg.	N.D.
Lilly's ext.............	neg.	neg.	+	neg.	N.D.
Pork muscle...........	neg.	neg.	neg.	N.D.	N.D.
Beef muscle..........	neg.	neg.	neg.	N.D.	N.D.
House dust............	neg.	neg.	neg.	N.D.	N.D.
Ragweed..............	neg.	neg.	N.D.	N.D.	N.D.

N. D.—not done.

Positive intradermal reactions to liver extract have been reported [29] with dilutions up to 1 : 100,000. Positive skin tests have persisted as long as one year after the occurrence of the allergic reaction.[10] Immediate [7, 10, 16] and delayed [9] generalized reactions from intracutaneous testing have occasionally been extremely severe. One of these immediate reactions, after the intradermal use of 0.1 c.c. undiluted extract, consisted of a tremendous local

edema and redness, in addition to nausea, diarrhea, and weakness.[16]   Harten and Walzer [18] have pointed out that "the danger of employing 0.1 c.c. for intracutaneous testing in such cases is obvious."

Precipitins and anaphylactic antibodies have been searched for in a few instances.[11, 29, 34, authors]   In Criep's one case [29] precipitins to liver extract were present in serum dilutions up to 1 : 100, but anaphylactic antibodies were not demonstrable.   Gigante [11] was also unable to demonstrate them in either of his two cases.   Taylor and Hilger [34] found precipitins in the serum of both their patients.   We were unable to get a single positive precipitin reaction to three different makes of liver extract even with undiluted serum from the three patients whose blood we investigated (table 1, cases 1, 2, 3).

Cause.   The cause of reactions to liver extract injections is not entirely clear, and it is likely that there is more than one type of reaction.   We agree with Harten and Walzer [18] that "there is little doubt that some of the cases which have been reported as allergic reactions to liver extract really belong in the group of histamine-like reactions."   Heinsen,[45, 46] in Germany, and Clark,[36] of the Lederle Laboratories in this country, have found histamine or a histamine-like substance in many batches of liver extract used commercially.   Choline-like substances have also been demonstrated.[36, 47]   Certain cases described in the literature [1, 24, 48, 49, 50] and possibly case 3 in this paper appear to be of this type.

The large majority of the reactions following liver extract injection or ingestion are undoubtedly true allergic reactions.   This opinion is based mainly on the clinical picture, with the positive intradermal tests and the presence of reagins and precipitins as corroborative evidence.   A question of considerable theoretical interest is whether the sensitivity is to liver as an organ or to the biological source; i.e., to the animal from which the liver was obtained.   Sixteen patients showing allergic reactions to liver extract were carefully studied with this problem in mind.[2, 20, 29, 33, 34, authors]   All had positive intracutaneous reactions to various brands of liver extract, and many had positive passive transfer reactions additionally.   These patients were all tested with the muscle protein extracts, and in some cases with the serum, of the animals (swine and beef) from which liver extracts are prepared commercially.   In every instance, with one exception—a patient incidentally allergic to beef—negative reactions were obtained, indicating that the sensitivity is to liver as an organ and not to the animal species.   Feinberg, Alt, and Young,[33] who studied eight of these patients, go even further and state: "The [allergic] specificity appears to be due to a special organ [liver] fraction not found with the ordinary protein but associated with the anti-anemic fraction."   In the present state of our knowledge concerning the chemistry of the anti-anemic fraction, that would appear to be merely an assumption, although we can be reasonably certain that the sensitivity is to some substance in liver, irrespective of its biological source.   Hypersensitiveness to the liver allergen cannot be produced at will, even in allergic patients, as Criep has demonstrated.[29]

Treatment. The symptomatic treatment of allergic reactions to liver extract is simple: adrenalin or ephedrine and calcium preparations for the generalized type, and in addition local applications, such as calamine lotion with phenol, for urticaria or pruritus. The avoidance of reactions presents a more difficult problem. Perhaps Tausk [51] is correct in saying that it may be "possible to avoid these reactions when the anti-anemic substance has been isolated in pure state." However, up to the present, even with marked concentration of the anti-anemic factor in certain liver extracts, the reactions have not been eliminated nor do they seem to be less frequent. It is our impression, from a review of the literature and from observation of our own cases, that without the therapeutic measures to be discussed, patients allergic to liver extract can tolerate the intramuscular injection of only approximately a certain number of units of anti-anemic substance, irrespective of whether it is administered in dilute or in concentrated form. Thus certain patients who usually have a reaction from 0.2 c.c. of an extract containing 20 units per c.c.—a total of 4 units—will probably have a similar reaction from 4 c.c. of an extract containing 1 unit per c.c.—again a total of 4 units. This is by no means an invariable rule; and as pointed out earlier, with the majority of patients allergic to liver, it is impossible to predict when an allergic reaction will develop. However, those few patients (such as our case 2) who usually do react to a certain number of units of anti-anemic substance and who usually do not react to a lesser number, irrespective of the concentration, tend to substantiate the contention that "the specificity appears to be due to a special organ [liver] fraction not found with the ordinary protein but associated with the anti-anemic fraction." [33]

The simplest method of avoiding reactions is the discontinuance of liver extract, which may be done when the patient does not have primary anemia. Changing to oral preparations may help to avoid reactions, but it is generally agreed that the oral treatment of primary anemia is not so effective as the intramuscular. Taylor and Hilger [34] recommend the use of histaminase. The intradermal tests with liver extracts were "definitely less pronounced" in their two patients while they were taking histaminase. However, they did not show that the clinical reactions were thus reduced, and one would not like to have to administer that preparation during all the years of liver extract therapy in cases of primary anemia. A more useful and feasible therapeutic agent for those patients who react frequently might be histamine in gradually increasing subcutaneous doses. This procedure has been shown [52, 53, 54] to produce a histamine refractoriness and to ameliorate or eliminate many allergic conditions.

Finally, there is the question of desensitization with gradually increasing doses of diluted liver extract. Many authors [1, 4, 7, 10, 13, 14, 20, 32] have claimed good results with this method; and we feel, from a study of those reports and especially from close observation of two of our patients (cases 1 and 2), that this is an excellent method for those patients who react regu-

larly or frequently. Naturally there have been occasional failures,[16, 27] as with any therapeutic procedure in clinical medicine. In the technic of desensitization there has been much variation. Engel[16] started with a 1 : 1,000,000 dilution, and Pache[20] with a 1 : 100,000,000 dilution. On the other hand, Andrews[32] started with minute amounts of undiluted extract; but from his description of the case, it appears to us that he would probably have achieved better progress had he used diluted extract at the beginning, although the final result was excellent. We began desensitization in our two cases with 0.1 c.c. of a 1 : 10 dilution and increased by about 0.2 c.c. every second or third day for about three weeks until the patients were receiving the average full therapeutic dose (Lederle's extract 3 c.c. or Reticulogen 0.5– 1.0 c.c.). We believe it important to keep this type of patient "desensitized" by giving the therapeutic injections in smaller quantities and at more frequent intervals than is customary; i.e., at least once a week.

Of course, it is necessary to attempt desensitization only in those patients who react regularly or frequently. For those who have one reaction and never another, such as our case 3, no such measure is needed. One should always have adrenalin, a sterile syringe and needle, and a tourniquet at hand when giving liver extract or any other biological product by injection. Although we favor an attempt at desensitization in certain patients, it is only fair to point out that "the results obtained by this method should be subject to guarded interpretation,"[18] since "spontaneous loss of sensitivity may explain the reports of successful, complete desensitization which occasionally appear in the literature."[40]

SUMMARY AND CONCLUSIONS

1. A review of the literature of allergic reactions to liver extract has been presented, and 11 additional cases have been reported.

2. The make of extract and the dose have little relation to the occurrence of such reactions.

3. Reactions usually occur after numerous well-tolerated injections, especially after a long injection-free interval.

4. The clinical manifestations are extremely varied, including practically every allergic sign and symptom.

5. Direct and indirect intracutaneous tests with various brands of diluted extract are usually positive, whereas similar tests with hog and beef muscle are usually negative.

6. Although a small number of the reported reactions are probably due to preformed histamine, the large majority are on a true allergic basis.

7. The sensitivity is to some substance—possibly the anti-anemic factor —in liver extract, irrespective of its biological source (hog, beef, etc.).

8. Desensitization with gradually increasing doses of diluted liver extract is recommended for patients who react frequently.

Addendum. Since this article was accepted for publication, another paper has appeared which gives a good review of this topic (FEINBERG, S. M., ALT, H. L. and YOUNG, R. H.: Allergy to injectable liver extracts: clinical and immunological observations, ANN. INT. MED., 1943, xviii, 311). Also two additional cases of unusual allergic reactions to liver extract have been brought to our attention. One was an allergic patient who was tested intradermally with liver extract and within a few minutes developed a severe anaphylactic shock, almost fatal. The other was a patient who became comatose and subsequently developed a hemiplegia shortly after an injection of liver extract. The opinion of several clinicians was that the injection was the direct cause of a cerebro-vascular accident of an allergic nature.

BIBLIOGRAPHY

1. MURPHY, W. P.: The parenteral use of liver extract in pernicious anemia, Jr. Am. Med. Assoc., 1932, xcviii, 1051.
2. JONES, C. A.: Allergic reactions following the parenteral administration of liver extract, Internat. Clin., 1939, iii, 258.
3. DIEFENBACH, W. E., and YUSKIS, A. S.: Allergy to liver extract, California and West. Med., 1939, 1, 28.
4. KRANTZ, C. I.: Anaphylactic reactions following medication with parenteral liver extract, Jr. Am. Med. Assoc., 1938, cx, 802.
5. HELD, I. W., and GOLDBLOOM, A. A.: Addison-Biermer's anemia (pernicious anemia): report of case showing allergic-like phenomena to liver extract, Jr. Am. Med. Assoc., 1931, xcvi, 1361.
6. CHAUDHURI, B. M.: Urticarial rashes after Campolon injection, Calcutta Med. Jr., 1936, xxx, 731.
7. DIENA, D.: Ipersensibilita a preparati epatici, Gior. d. r. Accad. di med. di Torino, 1938, ci, 462.
8. MARKOFF, N.: Zur Kenntnis einiger Arzneimittelüberempfindlichkeiten, Schweiz. med. Wchnschr., 1938, xix, 1016.
9. LASCH, F.: Über allergische Symptome bei parenteraler Lebertherapie, Wien. med. Wchnschr., 1936, lxxxvi, 126.
10. GRÜN, G.: Ueberempfindlichkeit gegen parenteral verabreichte Leberpräparate bei einem Fall von perniziöser Anämie, Wien. klin. Wchnschr., 1934, xlvii, 751.
11. GIGANTE, D.: Ipersensibilità agli estratti di fegato, ricerche cliniche e sperimentali, Minerva med., 1939, i, 582.
12. SÜSS: quoted by GIGANTE, D.[11]
13. CORELLI, F.: quoted by GIGANTE, D.[11]
14. MILBRADT, W.: Über eine eigenartige scheinbare Allergie gegen Leberextrakt, Dermat. Wchnschr., 1935, ci, 1595.
15. STRANDELL, B., and HAMMAR, E.: Magenresistente Fälle von Anaemia perniciosa, erfolgreich mit Campolon behandelt. Urtikaria als Komplikation, Acta med. Scandinav., 1932, lxxvii, 345.
16. ENGEL, K.: Anafilaxia a los Preparados de Higado en un caso de Anemia Perniciosa, Bol. assoc. med. de Puerto Rico, 1933, xxv, 326.
17. HAFSTRÖM, T. G.: Anafylaktisk chock i samband med heptomininjektion, Svenska läk.-tidning., 1937, xxxiv, 927.
18. HARTEN, M., and WALZER, M.: Allergy to insulin, liver, pituitary, pancreas, estrogens, enzymes, and similar substances, Jr. Allergy, 1940, xii, 72.
19. VON HERFF, D.: Die klinische Bedeutung der Arzneimittel als Antigene. Sogenannte Arzneimittelidiosynkrasien, 1937, G. Thieme, Leipsig.
20. PACHE, H. D.: Beobachtungen bei einer Allergie gegen Leberextrakte, Deutsch. med. Wchnschr., 1939, lxv, 1192.

21. Parrisius, W., and Lohmeyer, A.: Behandlung der perniziösen Anämie mit injizierbaren Leberextrakten, Tung-Chi med. Monatschr., 1933, viii, 191.
22. Segerdahl, E.: Om behandlung av perniciös anämi med intermittenta leverextraktinjektioner, Svenska läk.-tidning., 1934, xxxi, 1706.
23. Geijskes, P. A. G.: Onaangename Verschijnselen na Toediening van Pernaemon, Nederl. tijdschr. v. geneesk., 1936, lxxx, 1915.
24. Kuipers, F. C.: Overgevoeligheidsreactie Na Leverinspuiting, Nederl.. tijdschr. v. geneesk., 1935, lxxix, 2771.
25. Roovers, J. J. C. P. A.: Onaangename Verschijnselen Na Pernaemoninspuitingen, Nederl. tijdschr. v. geneesk., 1935, lxxix, 5148.
26. Bloom, M.: Sensitivity to liver extract, Jr. Am. Med. Assoc., 1935, cv, 223.
27. Queries and Minor Notes: Sensitivity to liver preparations, Jr. Am. Med. Assoc., 1940, cxv, 1121.
28. Gray, I., and Bowman, K. L.: quoted by Harten, M., and Walzer, M.[16]
29. Criep, L. H.: Allergy to liver extract, Jr. Am. Med. Assoc., 1938, cx, 506.
30. Feinberg, S. M.: Allergy to therapeutic substances, Illinois Med. Jr., 1941, lxxx, 244.
31. Murphy, W. P.: Maintenance of normal blood in pernicious anemia by means of intramuscular injections of a solution of liver extract, Am. Jr. Med. Sci., 1933, clxxxvi, 271.
32. Andrews, C. T.: Allergic reaction to liver extract, Lancet, 1941, i, 664.
33. Feinberg, S. M., Alt, H. L., and Young, R. H.: Allergy to injectable liver extract, Proc. Inst. of Med., Chicago, 1942, xiv, 87.
34. Taylor, C. B., and Hilger, D. W.: The use of histaminase by mouth in preventing systemic reactions to parenteral liver extract, Jr. Am. Med. Assoc., 1941, cxvii, 1880.
35. Bynum, W. T.: Allergy to liver extract, Jr. Oklahoma State Med. Assoc., 1941, xxxiv, 55.
36. Clark, G. W.: Personal communication.
37. Personal communication.
38. Matzger, E.: Bronchial asthma caused by liver and liver extract diet in a patient suffering from primary anemia, Jr. Am. Med. Assoc., 1931, xcvi, 110.
39. Gardner, J. W.: Allergy to oral administration of liver concentrate, Jr. Am. Med. Assoc., 1938, cx, 2003.
40. Moll, H. H.: The occurrence of polycythaemia and the value of liver therapy in asthma, Brit. Med. Jr., 1932, i, 976.
41. Rowe, A. H.: Clinical allergy due to foods, inhalants, contactants, fungi, bacteria and other causes: manifestations, diagnosis and treatment, 1937, Lea and Febiger, Philadelphia.
42. Schlesinger, W.: Zur Frage der Leberbehandlung bei pernizioeser Anaemie als diaetetischer Reiztherapie, Wien. med. Wchnschr., 1930, lxxx, 696.
43. Criep, L. H.: Allergy to pancreatic tissue extract, with report of two cases, Jr. Allergy, 1941, xii, 154.
44. Allin, R. N., and Meyer, O. O.: The development of eosinophilia following liver therapy, Jr. Lab. and Clin. Med., 1940, xxvi, 457.
45. Heinsen, H. A.: Chemische Untersuchungen an Leberpraeparaten des Handels auf kreislaufwirksame Substanzen, Klin. Wchnschr., 1933, xii, 1722.
46. Heinsen, H. A., and Wolf, H. J.: Der Einfluss koerpereigener Substanzen auf den Bludruck beim Menschen: IV. Die Wirkung von Leberpraeparaten bei intravenoeser Verabreichung, Klin. Wchnschr., 1934, xiii, 523.
47. Koops, W. S., Dingemanse, E., and Luwisch, D.: Ueber Blutdruckbeeinflüssende Stoffe in Leberpraeparaten, Acta brev. Neerland., 1935, v, 70.
48. Vaughan, W. T., and Pipes, D. M.: On the probable frequency of allergic shock, Am. Jr. Digest. Dis., 1937, iii, 558.
49. Queries and Minor Notes: Possible sensitivity to liver extract, Jr. Am. Med. Assoc., 1935, civ, 2019.

50. KLINHERT, D.: Onaangename Verschijnselen Na Pernaemoninspiuting, Nederl. tijdschr. v. geneesk., 1935, lxxix, 5751.

51. TAUSK, M.: Bijreacties Na Inspuiting van Leverextracten, Nederl. tijdschr. v. geneesk., 1936, lxxx, 748.

52. FARMER, L.: Histamine in anaphylaxis and allergy, Bull. New York Acad. Med., 1940, xvi, 618.

53. FARMER, L.: The histamine treatment of allergic diseases. I. Asthma and vasomotor rhinitis, Jr. Lab. and Clin. Med., 1941, xxvi, 802.

54. FARMER, L., and KAUFMAN, R. E.: Histamine in the treatment of nasal allergy (perennial and seasonal allergic rhinitis), Laryngoscope, 1942, lii, 255.

THE MANAGEMENT OF PAROXYSMAL TACHYCARDIA INCLUDING THE USE OF MECHOLYL *

By Philip W. Morgan, M.D., F.A.C.P., *Emporia, Kansas*

Paroxysmal supraventricular tachycardia is a common functional heart disorder of all ages but particularly of young adults without organic heart disease. Relatively few attacks are seen by physicians, since attacks cease spontaneously or the patient has learned ways of stopping them. Of the persons seeking medical aid for this arrhythmia, a few find their attacks resist ordinary physical means and oral therapy and persist for hours and sometimes many days before they spontaneously cease. Deaths have been recorded,[3] as have hemiplegia and gangrene[9] as thrombotic sequelae of the low pulse pressure and minute output during such attacks. A history of paroxysmal tachycardia rejects applicants for army air crew and flying personnel and electrocardiographic evidence is cause for rejection of army officer candidates,[1] but since first attacks are common in young adults it is probable that Army Surgeons will occasionally have to manage such problems.

Advice for the prevention of attacks is principally directed to extracardiac somatic factors and these vary with the individual patient. If drugs are indicated because attacks are frequent and tend to persist and annoy the patient, quinidine is best, but an occasional patient responds better to digitalis. Sedatives are helpful in the physician's program of reassurance, and sometimes are all that is required when observant patients realize that a contemplated experience may precipitate an attack. A typical example was that of a young college instructor who told me several years ago that he was subject to attacks when he traveled to see his sweetheart whom his family disliked as much as her family disliked him, but that the attacks could be prevented by 15 grains of bromides.

It is recognized that the psychic factor is a great one in these problems from several angles. It may act as a direct precipitating factor for attacks and a healthy person may develop an incapacitating neurosis because of ill founded notions of the significance and prognosis of his disorder. Reassurance, therefore, must be definite and backed by proved ability to terminate attacks as promised. The published facts are that people have been known to have attacks for over 50 years and have no influence on longevity, and if organic heart disease exists the prognosis depends on the underlying heart disease.[4]

A healthy vigorous man of 73 told me that he had had attacks occasionally for 30 years and had learned long since to disregard them. His son, 50, was just becoming convinced after five years' similar experience that his

---

* Presented at the Mid-Central States Regional Meeting of the American College of Physicians, Kansas City, Missouri, May 8, 1943.

attacks were no cause for concern. He knows carotid sinus pressure stops them and that 1½ grains of digitalis every second day will prevent them and that quinidine is less effective. Some form of carotid sinus reflex elicitation will stop the majority of attacks. The patient deserves to be carefully instructed in carotid sinus pressure, ocular pressure, the Mueller and Val Salva experiments and told about the benefits of postural change and vomiting. These six physical procedures in addition to some schemes which his experience may have taught him provide an armamentarium which in itself offers more than passive reassurance. Pressure on the eyeballs has to be enough to cause the patient some discomfort and the patient should look down while pressure is exerted. The Mueller and Val Salva experiments are easy for the patient to execute without notice, since in one the patient strains to exhale but keeps his glottis closed and in the other he strains to inhale but keeps his glottis closed. Various combinations of these procedures have caused slowing of paroxysmal fast heart rates when single procedures have failed. To induce vomiting, apomorphine has been used and syrup of ipecac in doses of from one to four drachms [9, 19] has been a favorite of some good clinicians as a treatment of attacks.

When the physical methods have been tried or before trying them the patient can be instructed to take his usual dose or a double dose of quinidine at two hour intervals for two or three doses or until tinnitus is noticed. In this manner patients have tolerated as much as 100 grains in one day.[19] If there is any tendency for him to develop an apprehensiveness, he should be provided with an effective sedative which he can take early in the attack and allow himself to assume a semirecumbent or recumbent position unless he knows that such positions tend to bring on attacks.[5] It has been thought that not until such procedures have been well tried and heart tones are becoming less vigorous or signs of basal râles or very annoying systemic signs have appeared was one justified in using parenteral quinidine or mecholyl or intravenous strophanthin or digitalis. One reported attack of 10 days' standing, several years ago, was stopped when quinidine had failed with 15 cat units of digitalis intravenously.[22] Just recently intravenous metrazol has been used with satisfactory results.[2] Intravenous quinidine is frequently referred to in the literature but I have encountered no reliable available preparation for this purpose. Just recently Sturnick, Riseman and Sagall [16] pointed out that "soluble preparations of quinidine sulphate for parenteral administration have not been readily available." This statement is true despite the fact that solutions of quinine dihydrochloride are commercially available in ampoules and have been administered intramuscularly and intravenously and dilute solutions of quinidine sulphate in dextrose or water and suspension of quinidine sulphate tablets in hot water and hydrochloric acid have been used in emergencies.[21] Sturnick, Riseman and Sagall [16] published their experiences with a preparation recommended by the Cinchona Products Institute, but the preparation requires more than average facilities since sterilization was achieved by passage through a Berkefeld filter. If the

preparation could be made commercially available it would apparently be an improvement over quinidine preparations now in use. The drip method of intravenous quinidine administration is the safest but it takes such a long time that one can wonder whether it was quinidine or the passage of time which stopped the tachycardia.[12] In the choice of any heroic procedure it is comforting to know that the effects of the drug can be quickly stopped at any moment and in that regard mecholyl has an advantage over the others.

For terminating attacks mecholyl, now council accepted for this purpose, is advised in the War Department's Technical Manual entitled "Notes on Cardiology in Aviation Medicine," and it has received increasingly favorable mention in the literature since first described for this purpose by Starr in 1933.[18] Detailed comment on the drug's history, its action and a practical scheme for its use have been omitted from most articles concerning the treatment of paroxysmal tachycardia.

The use of the various cholines has been a development of the present age. Acetylcholine was first synthesized by Baeyer in 1867 but had only a chemical interest. In 1914 Dale noted that the chemical mimicked the effects of stimulation of the parasympathetic nerves. Starr and others later made investigations which have provided a sound basis for the use of available cholines in medicine.[6] Acetyl-beta-methylcholine or mecholyl is one of the few cholines stable enough and with sufficient investigation behind it to deserve a place in our therapeutic armamentarium. When it reaches the tissues it is probably in a form which duplicates products of the body itself. Its greatest usefulness is in treating paroxysmal supraventricular tachycardia, and it has no place in treating other arrhythmias. It has been used in persons of all ages from infancy to old age. Atropine or epinephrine will abolish its effects and quinidine tends to block its action. Oral administration has been unsatisfactory either to prevent or stop attacks.[6, 13] Mecholyl should never be given intravenously, since the effects of hypodermically administered therapeutic doses are so rapid and dramatic that anyone who has not been appraised of them should familiarize himself well with the effects, and should not undertake to use the drug unless he follows very carefully a set procedure. However, if this is done, the physician can avail himself of an effective agent which he can control at will.[12, 18]

I have had only a few patients whose attacks have failed to respond as desired to oral quinidine, sedatives and the physical measures mentioned, but I decided to use mecholyl on resistant electrocardiographically proved supreventricular tachycardias after a visit to Dr. Starr's Clinic several years ago. Though I have employed it in treating only 12 attacks, the effect has been so uniform and in accord with the descriptions of the investigators that I feel the drug merits wider use. Even among competent internists I have encountered a sense of fear and hesitation when use of this drug is mentioned. Starr has always advised that in giving mecholyl "one should have a syringe of atropine ready for intravenous administration" but lately adds that he has not had to use it for many years, since he simply applies a tourniquet above

the site of injection when the action appears excessive as shown by nausea and vomiting. Since the effect of mecholyl on the bronchial tree is to cause bronchial spasm, it has been suggested that in asthmatic subjects the drug be either not used or else even greater care than usual be employed. In hyperthyroid patients mecholyl is capable of inducing auricular fibrillation and for this reason hyperthyroidism is sometimes considered a contraindication for this therapy though Starr has noticed no ill effects from mecholyl in such cases.[6, 12]

The patient receiving mecholyl should be recumbent, since the erect posture at the height of the drug's action may cause fainting. A bed pan should be ready for the same reason in case the subject should have a sudden desire to defecate during the drug's action [6] which is a possibility though none of my patients has had more than active audible peristalsis.

It is well to explain to the patient and to any relatives who insist on being present during the treatment each of the subjective and objective manifestations of the mecholyl effect before giving the injection. In less than a minute a brilliant flush comes in a wave over the blush areas, perspiration and salivation are profuse, and peristalsis becomes audible. Even if appraised before, the patient usually makes some comment concerning these things because they come so quickly. A medical colleague whose tachycardia I terminated with mecholyl without a previous sedative was so impressed that he decided to refer any resistant tachycardias for such therapy, and he volunteered the suggestion that the use of such a drug should be in the hands of someone other than a general practitioner such as himself. Having used the drug both with and without the previous administration of a sedative, I believe it is better to administer something to dim slightly the perceptive senses before using mecholyl. For this I have used a therapeutic dose of morphine sulphate. I have recently discussed this with Dr. Starr who says it is perfectly proper and who, although he has not used a sedative, is interested in the idea.[12] So with the patient and nurse or relative posted on coming events and contraindications considered and a sedative in effect, one can proceed.

The average dose of mecholyl for adults is 20 to 50 milligrams and it is available in sealed glass ampoules of the dry drug each containing 25 milligrams. The contents of each ampoule are easily soluble in 1 c.c. or less of sterile distilled water introduced into the ampoule. So that no confusion arises one can either use differently marked syringes or place the empty mecholyl ampoule over the needle of the syringe filled from it. Atropine gr. $\frac{1}{50}$ in solution ready for intravenous injection is in the second syringe. The arm with easily accessible veins is selected and a blood pressure cuff is applied or good tourniquet placed loosely high on the upper arm. Mecholyl is then administered subcutaneously below or distal to the blood pressure cuff which is not inflated. At the moment the heart rhythm and rate return to normal as detected by the stethoscope over the precordium, the blood pressure cuff is inflated to prevent further absorption and to make a vein ready if desired for

the administration of atropine.   The return to sinus rhythm has occurred in
my experience as early as 80 seconds following the mecholyl injection and
has been reported in less time.   If no effect on rate is noted by the time the
drug is at its peak effect as manifested by flush in the blush areas, perspira-
tion, salivation and loud peristalsis (2 to 10 minutes) Starr has suggested
massage of the site of injection and also carotid sinus stimulation by one of
the above physical means.[13]   This is necessary in some 20 per cent of cases.
If no effect is manifest 30 minutes after the injection, another dose can be
given.   The drug does not lose its effectiveness by repeated use as indicated
by a report of its successful use in stopping 15 of 16 attacks recurring in a
child over a two year period.[23]   I have had a similar successful experience in
eight attacks out of nine in a middle-aged woman over a three year period.
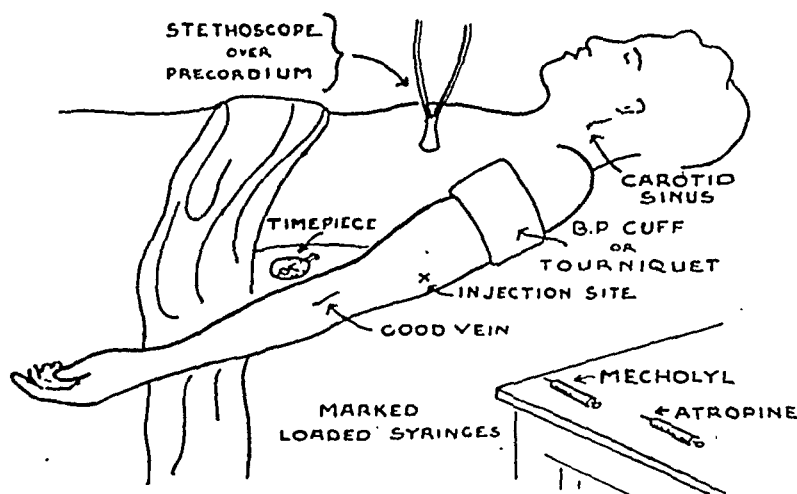
FIG. 1.   Mecholyl administration; patient recumbent.

The first time it was used on this patient it was ineffective because only 25
milligrams were given and no second dose was used and later experience
demonstrated that 40 to 45 milligrams were needed.   On several occasions
she had 8 to 10 grains of quinidine within three hours of satisfactory
mecholyl treatment, which supports the statement that mecholyl can break
through the quinidine effect.   The reliability and short time necessary to
abolish the tachycardia which this woman has been having occasionally for
25 years have made her grateful.   Most of her attacks cease spontaneously
or with repeated oral doses of quinidine, but if they persist for a few hours
she now has them stopped whereas previously she has been incapacitated at
least a day or two.   In a middle-aged man whose attack had resisted usual
therapy for 10 hours a second dose of 60 milligrams reinforced with carotid
pressure was given with success after one of 40 plus carotid sinus stimula-
tion plus massage of the site of injection had failed.

No deaths have been reported from the use of the drug, but reports are available of great overdose (10 and more times the therapeutic dose) and mistaken intravenous administration and in each instance recovery was complete.

Each of my patients' rhythm was proved electrocardiographically but I was not fortunate enough to secure a tracing during the transition to normal sinus rhythm. Such tracings have been published[18] and support what one hears with the stethoscope. In each attack that I have treated with mecholyl the rapid rhythm was interrupted by a brief period of asystole, then the next few beats seemed slightly slower than the normal sinus rhythm which was quickly established. The quick transition from a heart rate of 160 to 180 to one of 70 or 80 with the brief asystole is usually noted by the patients, though the relief from the rapid rate is ample reward for the brief moment of what they have termed a "funny feeling."

SUMMARY

1. Paroxysmal supraventricular tachycardia is a common functional cardiac abnormality usually seen in normal hearts but has been fatal and has led to disabling thrombotic conditions. A history of it disqualifies for air crew and flying personnel, and electrocardiographic evidence is cause for rejection in candidates for army commissions, but since the first attack may occur at any age it is probable that cases will be observed occasionally in our armed forces. Most attacks do not require medical attention, but it is estimated that 10 to 20 per cent defy the patient's efforts to stop them.

2. To prevent attacks direct therapy is usually not indicated, but attention is given extracardiac somatic factors; reassurance to the patient and investigation of psychic factors are indicated; if drugs are desired quinidine sulphate is most effective, digitalis is occasionally more satisfactory, and sedatives usually help.

3. Therapy of attacks: Carotid sinus reflex elicitation; sedatives; oral quinidine. If the latter is ineffective, digitalis has been used either orally or parenterally, but mecholyl is perferred if parenteral therapy is indicated.

4. Advantages and steps in the use and control of mecholyl are outlined and cases cited.

BIBLIOGRAPHY

1. Army Regulations: A.R. 40–105; 39, l.c.; —A.R. 40–110 20a 2 MRL-9 64d., TM 8–305.

2. BOYD, W. W.: Metrazol in auricular paroxysmal tachycardia, South Carolina Med. Assoc. Jr., 1942, xxxviii, 307–344.

3. COOKE, W. T., and WHITE, P. D.: Prognosis in paroxysmal tachycardia and paroxysmal auricular fibrillation, Brit. Heart Jr., 1942, iv, 153–162.

4. CAMPBELL, ELLIOTT: Paroxysmal tachycardia: etiology and prognosis of one hundred cases, Brit. Heart Jr., 1939, i, 123.

5. FRUE, M. JAMES, and MILLER, RALPH: Orthostatic paroxysmal auricular tachycardia with unusual response to change of posture, Am. Heart Jr., 1940, xx, 366.

6. Goodman, L., and Gilman, A.: The pharmacological basis of therapeutics, 1941, The Macmillan Company, New York.

7. Harrison, T. R.: Notes from refresher course, Kansas Heart Association of Kansas Medical Society, Oct., 1941.

8. Hubbard, J. P.: Paroxysmal tachycardia and its treatment in young infants, Am. Jr. Dis. Child., 1941, lxi, 687–709.

9. Levine, S. A.: Clinical heart disease, 1936, W. B. Saunders, Philadelphia and London.

10. Scherf, David: Notes from refresher course, Kansas Heart Association of Kansas Medical Society, 1939.

11. Scherf, David, and Boyd, Linn J.: Cardiovascular diseases, 1939, The C. V. Mosby Company, St. Louis.

12. Starr, Isaac: Personal communication, April 1943.

13. Starr, Isaac: Acetyl-B-methylcholin, III. Its action on paroxysmal tachycardia and peripheral vascular disease with a discussion of its action in other conditions, Am. Jr. Med. Sci., 1933, clxxxvi, 330.

14. Starr, Isaac, Elsom, K. A., and Reisinger, J. A.: Acetyl-B-methylcholin, I. The action on normal persons with a note on the action of the ethyl ether of B-Methylcholin, Am. Jr. Med. Sci., 1933, clxxxxi, 313.

15. Starr, Isaac: Acetyl-B-methylcholin; further studies of its action in paroxysmal tachycardia and in certain other disturbances of cardiac rhythm, Am. Jr. Med. Sci., 1936, cxci, 210–225.

16. Sturnick, Melvin I., Riseman, Joseph E. F., and Sagall, Elliott L.: Studies on the action of quinidine in man, Jr. Am. Med. Assoc., 1943, cxxi, 917.

17. Taran, L. M., and Jennings, K. G.: Paroxysmal atrioventricular nodal tachycardia in new-born infant, Am. Jr. Dis. Child., 1937, liv, 557–572.

18. Weiss, Soma, and Baker, James P.: The carotid sinus reflex in health and disease, Medicine, 1933, xii, 297.

19. Weiss, Soma, and Sprague, H.: Vagal reflex irritability and treatment of paroxysmal auricular tachycardia with ipecac, Am. Jr. Med. Sci., 1937, cxciv, 53–63.

20. White, P. D.: Heart disease, 1931, The Macmillan Co., New York.

21. White, P. D.: Tachycardia and its treatment, Modern Concepts of Cardiovascular Disease, 1940, lx.

22. Wilson, F. N.: Notes from refresher course, Kansas Heart Association of Kansas Medical Society, Oct. 1940.

23. Wright, F. H.: Paroxysmal nodal tachycardia in girl aged 8, Am. Jr. Dis. Child., 1938, lvi, 133.

TREATMENT OF SUBACUTE BACTERIAL ENDO-CARDITIS: CURRENT RESULTS *

By S. S. Lichtman, M.D., F.A.C.P., *New York, N. Y.*

Sulfonamide chemotherapy has proved disappointing in subacute bacterial endocarditis. Final judgment of its merit must be reserved, however, until the incidence of recovery in a large series of treated cases is compared with spontaneous recovery in the pre-sulfonamide era.

In a preliminary survey of 288 cases of subacute bacterial endocarditis treated by current methods, Lichtman and Bierman [1] deduced that chemotherapy and supplementary measures produced recovery in a small but significant percentage of cases. This survey has been continued with the aim of obtaining correct answers to the questions:

1. Is sulfonamide chemotherapy responsible for recovery in subacute bacterial endocarditis?

2. Do supplementary therapeutic measures, i.e., heparin, artificial hyperpyrexia, etc., enhance the results of chemotherapy?

Material

The cases previously reported [1] are here supplemented by reports in the literature, unpublished communications, and cases treated at The Mount Sinai Hospital up to April, 1942. The series now includes 98 cases of subacute bacterial endocarditis due to *Streptococcus viridans, Hemophilus influenzae* and enterococcus from The Mount Sinai Hospital and 606 cases collected from other sources, a grand total of 704 cases. Cases due to the gonococcus were not included; only adequately treated groups of cases were selected.† Seven recovered among the Mount Sinai cases,‡ and a total of 39 in the entire study. The material is presented under the headings:

Spontaneous recoveries reported in the literature.
Recovery with the use of sulfonamide drugs.
Recovery with the use of "combined methods," i.e., sulfonamide combined with heparin or fever therapy.
The results with other forms of treatment.

Spontaneous Recoveries: These are recorded in table 1. Libman's experience leads with four recoveries among 150 cases carefully studied and followed,[2] and subsequently 12 among 1,000,[2] and 22 among 1,500 cases.[8] Single recoveries have been reported by Horder in 150, by Kissling in 43, by Middleton and Burke in 88 cases, and also by Weber,[8] respectively. There were no spontaneous recoveries among 815 cases reported by other observers (table 1). The incidence of spontaneous recovery among 2,596 collected cases was 1 per cent.

TABLE I

Spontaneous Recoveries in Subacute Bacterial Endocarditis

	Number of Cases	Number of Recoveries
Libman [2]	1,500	22
Horder	150	1
Thayer	206	0
Warren and Herrick	25	0
Morrison [4]	145	0
Fulton and Levine [5]	111	0
Kissling	43	1
Schulten et al.[6]	200	0
Major	15	0
Middleton and Burke [1]	88	1
Middleton and McCue [7]	23	0
Steele	30	0
Herrell and Brown [9]	60	0
Total	2,596	25
Per cent Spontaneous Recovery	1.0	

Recovery with Sulfonamide Drugs: The results of sulfonamide chemotherapy are presented in table 2. Recoveries among *groups* of cases have

TABLE II

Results of Sulfonamide Chemotherapy in Subacute Bacterial Endocarditis

	Number of Cases	Number of Recoveries
Major	7	3 (Viridans)
Kinell and Ernstene	5	0
Spink and Crago	11	1
Klee and Romer	4	0
Ellis	2	0
Whitby	3	0
Bliss, Long and Feinstone	3	0
Kolmer	10	0
Steele	10	0
Long [7]	187	8 (Viridans)
Leach, Faulkner, Duncan & McGinn [10]	18	1 (Viridans)
Porter and White [10]	11	0
Middleton and McCue [7]	5	0
Herrell and Brown [9]	80	0
Field, Hoobler and Avery [11]	31	1 (Viridans)
Kinsella [12]	19	0
Heyer and Hick [18]	14	1
Bickel and Mozer [14]	8	2
Smith, Sauls, and Stone [20]	15	1
Mount Sinai	46	3 (2 Viridans; 1 *Hemophilus influenzae*
Total	489	21
Per cent Recovery	4.0	

been reported by Major,[1] Spink and Crago,[1] Long,[7] Leach et al.,[10] Field et al.,[11] Heyer and Hick,[13] Bickel and Mozer,[14] Smith, Sauls and Stone,[20] and in the Mount Sinai series.   Twenty-one recoveries were reported in a combined series of 337 cases and no recoveries in another combined series of 152 cases.   The incidence of recovery with the use of sulfonamides alone in a total of 489 cases was 4 per cent.

Isolated successfully treated cases have been reported by McQuarrie,[1] Barton and Stinger,[1] Lian and Frumusan,[15] Heyman,[1] Christie,[1] Christie and Parker,[16] Druckman,[17] Jersild,[18] and Andrews.[19]   Smith, Sauls and Stone[20] collected 35 reports of cures.

Recovery with Combined Methods of Treatment: A. *Chemotherapy and Heparin:* A total of 109 cases with seven recoveries belong in this group (table 3).   Recoveries in heparinized patients are listed by Kelson and White,[1] Leach et al.,[10] Kelson,[10] McLean et al.,[21] and one by us.   The incidence of recovery in the entire heparinized group was 6.5 per cent.   B. *Chemotherapy and Artificial Hyperthermia:* Sixty-one cases received artificial fever therapy.   Levine and Gibson[22] observed one definite recovery among 12 cases and another case is now apparently cured for three months.   Three patients observed by Bierman and Baehr[23] among 34 cases treated at The

TABLE III

Results with Combined Methods of Treatment of Subacute Bacterial Endocarditis

	Number of Cases	Number of Recoveries	Percentage of Recoveries
Chemotherapy, heparin			
Kelson and White[1]	7	2	
Leach, Faulkner, Duncan, McGinn	16	1	
Kelson[10]	20*	3**	
Field, Hoobler, Avery[11]	5	0	
McLean, Meyer, Griffith[21]	28***	1	
Herrell and Brown[9]	26	0	
Mount Sinai	13	1 (Viridans)	
	109	7	6.5
Chemotherapy, hyperthermia			
Krusen and Bennett	11	0	
Porter and White[10]	4	0	
Levine and Gibson[22]	12	1 (Viridans)	
Mount Sinai	34	3 (2 Viridans; 1 Hemophilus)	
	61	4	6.5
Chemotherapy, intravenous typhoid			
Solomon[21]	22	5 (Viridans)	
Porter and White[10]	3	0	
Middleton and McCue[7]	7	0	
Davidson and Shlevin[25]	8	2 (Viridans)	
Mount Sinai	5	0	
Total	45	7	15.5

Six * cases and one ** recovery of Mount Sinai Series included.
*** After deduction of cases already included in this table.

Mount Sinai Hospital recovered and now follow normal lives.* Two were
cases of *S. viridans* and one of *Hemophilus influenzae* endocarditis. The in-
cidence of recovery in 61 cases was 6.5 per cent (table 3).

Forty-five cases received combined sulfonamide chemotherapy and *intra-
venous typhoid vaccine*. Clinical recoveries from this method of treatment
have been observed by Solomon [24] and Davidson and Shlevin.[25] The in-
cidence of recovery among 45 cases was 15.5 per cent (table 3).

Miscellaneous Forms of Therapy: Middleton and Burke [1, 7] employed
radiotherapy in 12 cases and it was combined with sulfonamides in six cases
at The Mount Sinai Hospital without success. Radiotherapy was employed
in cases with recovery reported by Bierman and Baehr [28] and Smith, Sauls
and Stone,[20] but its effective value discounted in both instances.

TABLE IV

Summary of Results of Treatment of Subacute Bacterial Endocarditis

Method of Treatment	Number Treated	Number Recovered	Percentage Recovered
Sulfonamide Chemotherapy *			
Mount Sinai.............................	46	3 (2 Viridans; 1 Hemophilus)	
Literature.............................	443	18	
	489	21	4.0
Combined Therapy **			
Mount Sinai.............................	52	4 (3 Viridans; 1 Hemophilus)	
Literature.............................	163	14	
	215	18	8.5
Total Cases			
Mount Sinai.............................	98	7	7%
Literature.............................	606	32	5%
Total.............................	704	39	5.5%

* Sulfonamide compounds (sulfanilamide, sulfapyridine, sulfathiazole, sulfadiazine).
** Chemotherapy combined with (1) heparin, (2) radiotherapy, (3) hyperthermia, (4)
intravenous typhoid-paratyphoid vaccine.

Neoarsphenamine has been employed in over 70 cases. Osgood [26]
analyzed the protocols of 34 cases treated with this arsenical and listed four
recoveries. There were also 36 other cases without detailed protocols, six
of whom remained symptom-free for several months. The evaluation of the
status of neoarsphenamine therapy awaits the results of further trial.
Isolated failures have been noted by Middleton and McCue [7] and in the
Mount Sinai series.[1] Lippmann [27] reported a case of recovery after com-
bined sulfonamide and solarson (1 per cent ammonium heptenchlorarsonate)
therapy.

* Treated under the supervision of Dr. William Bierman, Physical Therapist to Mount
Sinai Hospital.

Dicoumarin, possessing heparin-like properties, has as yet been applied in too few cases to estimate its value as a substitute for heparin.

Surgical ligation of the ductus arteriosus in cases of subacute bacterial endocarditis superimposed on patent ductus arteriosus affords the best prospect of recovery of all the methods of treatment. Surgical procedure, however, is applicable only to the small number of cases of subacute bacterial endocarditis developing on the basis of this congenital anomaly. Recovery in well over 50 per cent of cases with patent ductus and subacute bacterial endocarditis is reported by Touroff et al.,[28] and by Gross.[29]

COMMENT

The phenomenal results of sulfonamide chemotherapy in the treatment of infections emphasize its relative failure in the treatment of subacute bacterial endocarditis. Even the occasional recovery from this disease following chemotherapy is viewed with skepticism, an attitude which is unwarranted since recoveries undoubtedly occur. To disclaim the authenticity of all recovered cases casts doubt also on the occurrence of spontaneous recoveries. In each recovery it is justifiable to deliberate whether the *Streptococcus viridans* is a secondary invader in a case of active rheumatic carditis,[30] or the microörganism in a septicemia without bacterial endocarditis.[31]

It is more consistent to accept recoveries in patients with the established clinical criteria of subacute bacterial endocarditis as authentic than to question the accuracy of diagnosis or the therapeutic result, on the general principle that recovery in this disease occurs rarely if ever. The recent increase in reported recoveries is probably due to early recognition and effective sulfonamide treatment of mild cases. Undue skepticism of results in this type of case thwarts the prospect of better results by early diagnosis and treatment. Recoveries may be few and far between, but an increased rate of recovery, no matter how small, represents a significant advance in treatment. A 3 per cent rise in recovery rate above the incidence of spontaneous recovery of 1 per cent means the survival of an additional 30 individuals in 1,000 cases. This is not phenomenal, but it represents a substantial triumph for the 30 survivors who are usually fit to return to normal life.

The incidence of spontaneous recovery may be accepted as approximately 1 per cent (table 1). Four per cent of patients with subacute bacterial endocarditis treated by sulfonamide chemotherapy appear to recover. The rate of recovery in patients treated both by a combination of sulfonamides and heparin and by sulfonamide and artificial hyperthermia was 6.5 per cent. The significance of the increase from 4 to 6.5 per cent of recovery may be questioned. Decision as to the value of heparin must be withheld until the results of treatment are compared with those in a series of cases in which bacteremia and fever have been reduced to nil by sulfonamide medication alone. Comparison will demonstrate whether heparinization influences recurrence of bacteremia once effectively sterilized by sulfonamide chemotherapy. Until this comparison is made the contention will constantly be

raised that the alleged favorable results of heparinization are due merely to selection of sulfonamide-cures for this form of treatment. The future of the use of heparin in this disease is further conditioned by many claims of an increased incidence of fatal cerebral hemorrhage and also by the fact that bacteremia is controlled at least temporarily by available sulfonamides in only approximately 10 per cent of patients with the disease. Since persistent bacteremia precludes the use of heparin, this form of therapy is restricted in its application.

The increase from 4.0 to 6.5 per cent recovery in sulfonamide-treated patients, supplemented by artificial fever therapy on the other hand, probably represents a truer increase in effectiveness of sulfonamide chemotherapy since hyperthermia produced results *after* failure of sulfonamide and other forms of treatment.[1]

Favorable response to artificial hyperthermia in *Hemophilus influenzae* endocarditis should not be discounted on the basis that this organism is especially thermosensitive. Bierman and Baehr [23] noted recovery in a case of subacute *Hemophilus* endocarditis treated by combined sulfonamide and fever therapy but a parallel case treated in the same manner at the same time failed to respond. The prognosis of endocarditis due to this organism is not materially different from *Streptococcus viridans* endocarditis.[32]

The unusually high incidence of recovery following the use of intravenous typhoid vaccine and sulfonamides is remarkable but it is doubtful that this degree of success will mark the results in a large series of cases so treated.

The results of surgical ligation of the ductus arteriosus in subacute bacterial endocarditis superimposed on the patent ductus are phenomenal. Surgical management of this form of endocarditis is accompanied by prompt surgical success in well over 50 per cent of cases. The choice between surgical and medical management of these cases is influenced by the following factors: immediate surgical death occurs in a small percentage of cases; sulfonamide cures are reported in a small but definite number of cases; fever persists and death from endocarditis ensues in some cases despite the ligation of the ductus and resulting negative blood cultures. In rare instances subacute bacterial endocarditis develops after prophylactic ligation of a patent ductus.[34] Occasionally the diagnosis of patent ductus or associated congenital lesions is erroneous or the vegetative process extends beyond the ductus arteriosus up to the aortic valve and aorta. In conservative hands, surgical ligation should be attempted promptly after failure of medical measures.

SUMMARY

The results of current methods of treatment of subacute bacterial endocarditis are disappointing; however, a small but significant number of patients recover. The recovery rate among a total of 704 cases was found to average 5.5 per cent. Of 489 cases treated by sulfonamide chemotherapy, 21 recovered, an incidence of *4 per cent;* among the remaining 215 patients treated by chemotherapy, supplemented by heparin or fever therapy, 18

recovered or 8.5 per cent. Of 109 heparinized patients, seven recovered, an incidence of *6.5 per cent.* Of 61 patients treated with artificial fever therapy, four recovered, an incidence of *6.5 per cent* recovery. The incidence of spontaneous recovery in subacute bacterial endocarditis is estimated at approximately 1 per cent.

Supplementary measures may increase the recovery rate in subacute bacterial endocarditis treated with sulfonamides. Artificial fever therapy supplementing sulfonamide chemotherapy produced a slight but significant increase in recovery rate from 4 to 6.5 per cent and intravenous typhoid vaccine appeared also to produce an increased recovery rate subject to further trial. The evaluation of heparinization as a supplementary measure of treatment requires further trial in properly controlled material. Surgical ligation performed on patients with patent ductus arteriosus complicated by subacute bacterial endocarditis produced the highest percentage of recoveries. Unfortunately, however, this cardiac anomaly occurs in only a minor number of cases of subacute bacterial endocarditis. An estimation of the therapeutic value of neoarsphenamine and dicoumarin awaits further trial.

Spontaneous recovery is acknowledged to occur in approximately 1 per cent of cases. Failure to encounter recovery in a large series of cases of subacute bacterial endocarditis treated by current methods does not justify the arbitrary blanket rejection of all published reports of recovery as spurious cases of subacute bacterial endocarditis. The factors responsible for individual recoveries cannot be formulated. Until methods of treatment and results are improved further, every patient with subacute bacterial endocarditis should receive intensive sulfonamide chemotherapy to tolerance. The choice of supplementary therapeutic measures rests at present with individual preference.

BIBLIOGRAPHY

1. LICHTMAN, S. S., and BIERMAN, W.: The treatment of subacute bacterial endocarditis: present status, Jr. Am. Med. Assoc., 1941, cxvi, 286.
2. LIBMAN, EMANUEL: A consideration of the prognosis in subacute bacterial endocarditis, Am. Heart Jr., 1925, i, 25. A further report on recovery and recurrence in subacute bacterial endocarditis, Trans. Assoc. Am. Phys., 1933, xlviii, 44.
3. LIBMAN, EMANUEL, and FRIEDBERG, C. K.: Subacute bacterial endocarditis, Cyclopaedia of Medicine, F. A. Davis, Philadelphia, 1939, iii, 660.
4. MORRISON, H.: Subacute bacterial endocarditis in Massachusetts General Hospital, Boston Med. and Surg. Jr., 1927, cxcvii, 46.
5. FULTON, M. N., and LEVINE, S. A.: Subacute bacterial endocarditis, Am. Jr. Med. Sci., 1932, clxxxiii, 60.
6. SCHULTEN, H.: Wass kann man bei Endocarditis lenta therapeutisch machen? Med. Klin., 1935, xxxi, 937.
7. Personal Communications: MIDDLETON, W. S., and McCUE, H.; LONG, PERRIN H.
8. WEBER, F. P.: Recovery from infection of subacute bacterial endocarditis without sulfonamides, Lancet, 1941, i, 630.
9. HERRELL, W. E., and BROWN, A. E.: Chemotherapy in the treatment of streptococcal infections, Minnesota Med., 1941, xxiv, 1059; and personal communication.
10. LEACH, C. E., FAULKNER, J. M., DUNCAN, C. N., McGINN, S., PORTER, R. R., WHITE,

P. D., and KELSON, S. R.: Chemotherapy and heparin in subacute bacterial endo-
carditis: further experiences, Jr. Am. Med. Assoc., 1941, cxvii, 1345.

11. FIELD, H., JR., HOOBLER, S. W., and AVERY, N. C., JR.: Results of chemotherapy in
subacute bacterial endocarditis, Am. Jr. Med. Sci., 1941, ccii, 798.

12. KINSELLA, R. A.: Chemotherapy of bacterial endocarditis, ANN. INT. MED., 1941, xv, 982.

13. HEYER, H. E., and HICK, F. K.: Experiences in the treatment of subacute bacterial endo-
carditis with sulfanilamide, sulfapyridine, and sulfathiazole; a review of previously
reported cured cases with the report of fifteen treated cases including one cure and
one aborted case, ANN. INT. MED., 1941, xv, 291.

14. BICKEL, G., and MOZER, J. J.: Endocardite lente et traitment sulfamide, Rev. méd. de la
Suisse, 1941, lxi, 474.

15. LIAN, C., and FRUMUSAN, P.: Endocardite maligne lente streptococcique et remission de
trois mois sous l'influence du 693 (Dagenan), Bull. et mém. Soc. méd. d. hôp. de Paris,
1940, lvi, 47.

16. CHRISTIE, A., and PARKER, A.: Subacute bacterial endocarditis treatment with chemo-
therapeutic agents, Clinics, 1942, i, 677.

17. DRUCKMAN, J. S.: A case of subacute bacterial endocarditis with apparent cure, Jr. Am.
Med. Assoc., 1941, cxvii, 101.

18. JERSILD, M.: Subacute bacterial endocarditis (endocarditis lenta) with apparent recovery
after treatment with sulfamethylthiazole, Ugesk. f. laeger., 1941, ciii, 1261.

19. ANDREWS, C. T.: Bacterial endocarditis; possibility of cure by sulfonamides, with report
of a case, Brit. Med. Jr., 1940, i, 5.

20. SMITH, C., SAULS, H. C., and STONE, C. F.: Subacute bacterial endocarditis due to
Streptococcus viridans, Jr. Am. Med. Assoc., 1942, cxix, 478.

21. McLEAN, J., MEYER, B. B. M., and GRIFFITH, J. M.: Heparin in subacute bacterial endo-
carditis, Jr. Am. Med. Assoc., 1941, cxvii, 1870.

22. LEVINE, S. A., and GIBSON, J. G., 2nd: Personal communication.

23. BIERMAN, W., and BAEHR, G.: The use of physically induced pyrexia and chemotherapy,
Jr. Am. Med. Assoc., 1941, cxvi, 292.

24. SOLOMON, H.: Subacute bacterial endocarditis: treatment with sulfapyridine and intra-
venous injections of typhoparatyphoid vaccine, New York State Jr. Med., 1941, xli, 45;
and personal communication.

25. DAVIDSON, A. G., and SHLEVIN, E. L.: Personal communication.

26. OSGOOD, E. E.: Neoarsphenamine therapy of bacterial infections, Arch. Int. Med., 1942,
lxix, 746.

27. LIPPMANN, K.: Subacute bacterial endocarditis case; new method of treatment, New York
State Jr. Med., 1940, xl, 524.

28. TOUROFF, A. S. W., and VESELL, H.: Subacute *Streptococcus viridans* endarteritis com-
plicating patent ductus arteriosus, Jr. Am. Med. Assoc., 1940, cxv, 1270.

TOUROFF, A. S. W., VESELL, H., and CHASNOFF, J.: Operative cure of subacute *Strepto-
coccus viridans* endarteritis superimposed on patent ductus arteriosus, Jr. Am. Med.
Assoc., 1942, cxviii, 890; and personal communication.

29. GROSS, R. E.: Personal communication.

30. LICHTMAN, S. S., and GROSS, L.: Streptococci in the blood in rheumatic fever, rheumatoid
arthritis and other diseases, Arch. Int. Med., 1932, xlix, 1078.

31. MOORE, G. B., and TANNENBAUM, A. J.: *Streptococcus viridans* septicemia, Jr. Am. Med.
Assoc., 1942, cxviii, 372.

NYE, R. N.: *Streptococcus viridans* septicemia, Jr. Am. Med. Assoc., 1942, cxviii, 917.

32. ROSE, H. M.: *Hemophilus influenzae* type A endocarditis, Am. Jr. Med. Sci., 1941, ccii,
187.

33. WILLIUS, F. A.: A talk on the hapless therapy of subacute bacterial endocarditis, Proc.
Staff Meet. Mayo Clin., 1942, xvii, 216.

34. SHAPIRO, M. J., and KEYS, A. B.: An analysis of the operative treatment of patent ductus
arteriosus, Annual Session American Medical Association, Atlantic City, June, 1942.

PSYCHOSIS DUE TO SULFONAMIDES *

By Roy E. Kinsey, Captain, M.C., *Camp Blanding, Florida*

Various toxic reactions to the sulfonamides have been described, and among the more uncommon manifestations of toxicity is psychosis. There are numerous cases of psychosis reported following the administration of sulfanilamide.[1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12] Long,[2] although listing the incidence of psychosis during the use of sulfapyridine at 0.3 per cent, states that no sulfathiazole psychosis has yet been reported. Brown, Thornton and Wilson[3] report delirium in seven patients of a series of 100 cases given sulfapyridine. Two cases received less than 25 grams and five received over 25 grams in less than 10 days. Wyrens[4] states that mental disturbances are uncommon following either sulfapyridine or sulfathiazole administration but does not quote any figures. During the past 13 months there have occurred in the Station Hospital at Camp Blanding, Florida, two episodes of psychosis during the administration of sulfonamides which I wish to report, as they occurred in patients under sulfathiazole and sulfadiazine therapy.

CASE REPORTS

Case 1. S. K., Private, white, male, aged 28, was admitted to the Station Hospital, Camp Blanding, Florida, April 8, 1941, weighing 145 pounds and complaining of having been ill one day with fever, sore throat, productive cough, chill, and generalized aching. His past history was non-contributory. On examination, the patient showed evidence of an upper respiratory infection with a temperature of 101.2° F., pulse rate 96, respiratory rate 20. The laboratory studies showed: urine normal, white blood cell count 12,900, hemoglobin 70 per cent, and red blood cell count 3.3 million. On the night of April 10 his cough became worse, and he complained of a pain in his chest. Physical examination showed evidence of consolidation of the left lower lobe, and sulfathiazole therapy was begun, the patient receiving two grams at the first dose and one gram every four hours thereafter. A roentgenogram on the following day confirmed the diagnosis of left lower lobe pneumonia, and the patient continued to receive one gram of sulfathiazole every four hours, the temperature returning to normal on April 11. The next day, on the afternoon of April 12, about 48 hours after the first dose of sulfathiazole, the patient became talkative, nervous and irrational. The drug was withdrawn, but 12 hours later the psychosis had advanced so far that the patient was delusional and hallucinated in the auditory and visual fields, requiring treatment in a closed psychiatric ward. On April 15, 72 hours after onset, he regained orientation, lost his hallucinations and delusions but remained somewhat apprehensive. By April 16 he had regained his normal mental state. In all, the patient received 13 grams of sulfathiazole over a period of 48 hours. At no time during the illness did the patient appear extremely intoxicated and his sensorium was clear during the febrile period, the delirium coming on after a 12 hour period of normal temperature. On recovery there was no memory of the psychotic episode. Unfortunately, in this case the type of the organism and blood sulfathiazole levels were not determined.

Case 2. B. O., colored, male, CCC, aged 17, weighing 125 pounds, was admitted on April 11, 1942, because of cough, chill, pain in his chest, fever and bloody sputum of 12 hours' duration. His past history was non-contributory. Physical examination showed a rather undernourished colored man in a moderate degree of toxemia, who appeared acutely ill. The heart was normal except for rapid rate and accentuated second pulmonic sound. Examination of the lungs revealed signs of consolidation in the right lower lobe, later confirmed by roentgenogram. The sputum showed pneumococci, type VII, with over 11 per high power field. The white blood cell count was 42,500, the hemoglobin 85 per cent, red blood cell count 5.0 million, and urinary findings normal. The temperature was 104° F., pulse rate 110, respiratory rate 36, blood pressure 105 mm. Hg systolic, and 66 mm. diastolic. Sulfadiazine was started at 4:00 p.m., April 11, 1942, the initial dose being four grams and one gram being given every four hours thereafter. His temperature returned to normal the following day, the patient feeling well and mentally clear. On the morning of the third day, approximately 40 hours after the first dose of the drug was given and after 24 hours of normal temperature, he awoke complaining that his father and brother had been shot and that he must go home at once. His reaction to this delusion was so great that he attempted to get out of the window. The drug was discontinued while the temperature was still normal, sulfadiazine blood level being 6.8 milligrams per 100 c.c. At this time the patient was oriented as to time, place and person, but a few hours later he became disoriented and had visual and auditory hallucinations. He heard the voices of his relatives and saw brightly colored objects such as green trucks, green snakes, green spiders and pink hats. Twenty-four hours after withdrawal of the drug, the blood level reached two milligrams per 100 c.c., and there was a recurrence of his pneumonia with temperature reaching 104° F. About four hours later, 28 hours after cessation of the drug, he became mentally clear with the temperature still 104° F. The patient received 14 grams of sulfadiazine in 40 hours, and his highest blood level was 6.8 milligrams per 100 c.c. After the recurrence of the pneumonia and clearing of psychosis, he was treated successfully with small doses of sulfathiazole instead of sulfadiazine. It may be noted here that as long as the sulfathiazole blood level was kept below 4.0 milligrams per 100 c.c., the patient was mentally clear, but when sulfathiazole blood level reached 5.2 milligrams per 100 c.c., the patient became delusional in the same manner as he did when under sulfadiazine administration. At the onset of this delirium, the patient was given large quantities of intravenous fluids and his delusions cleared within four hours, the blood sulfathiazole level receding to 4.0 milligrams per 100 c.c. within an hour after recovery. This delusional state occurred after the administration of 14 grams of sulfathiazole and approximately 60 hours after the initial dose. After recovery there was no memory of the psychotic episodes.

DISCUSSION

A search of the literature reveals a great number of cases of toxic psychosis precipitated by sulfanilamide but few from other sulfonamides. In the cases reported by Brown, Thornton and Wilson[3] occurring with sulfapyridine, delirium was most frequent in those who received over 25 grams in less than 10 days. In the two cases reported in this paper, the psychosis occurred within 48 hours of the first dose of the drug: in the case of sulfathiazole, after the administration of 14 grams; with the sulfadiazine, after 13 grams. I am not considering the recurrence of delusions in case 2 following the administration of sulfathiazole as an additional case report, but I would

like to bring out the fact that this delusional state occurred 60 hours after the first dose of sulfathiazole and after the administration of 14 grams of the drug.

It may be argued that in case 2 the psychosis was caused by the fever and other toxic effects of the pneumonia, but I do not believe that is the case as the psychosis occurred after the patient had been afebrile for 24 hours and cleared while the temperature was 104° F. with a recurrence of the pneumonia.

The psychosis in each case was quite similar, and both were actively delusional and hallucinated in auditory and visual fields. The psychosis in the first case lasted longer and was more violent.

SUMMARY

Two cases of psychosis following administration of sulfonamides are reported. Both cases occurred during the first 48 hours of treatment and after approximately the same amount of drug (sulfathiazole, 14 grams and sulfadiazine, 13 grams). The psychosis with sulfadiazine lasted 28 hours and with sulfathiazole 96 hours. Although there are too few cases reported to draw any accurate conclusions, one is led to believe that psychosis from the administration of sulfapyridine, sulfathiazole and sulfadiazine occur early. Both of the psychoses cleared without ill effects, although case 1 required treatment on a closed psychiatric ward and case 2 required constant attention.

CONCLUSION

1. Psychosis may occur following the administration of sulfanilamide, sulfapyridine, sulfathiazole or sulfadiazine.

2. When mental aberrations are noted, they are likely to be cumulative and must be carefully observed, as the patient is likely to become frankly psychotic.

BIBLIOGRAPHY

1. DANZIGER, LEWIS: Delayed toxic reaction to sulfanilamide. Case report, Bull. Johns Hopkins Hosp., 1938, lxiii, 340.

2. LONG, PERRIN H., HAVILAND, JAMES W., EDWARDS, LYDIA B., and BLISS, ELEANOR A.: The toxic manifestations of sulfanilamide and its derivatives with reference to their importance in the course of therapy, Jr. Am. Med. Assoc., 1940, cxv, 364–368.

3. BROWN, W., HURST, T. T., THORNTON, W. B., and WILSON, J. STUART: An evaluation of the clinical toxicity of sulfanilamide and sulfapyridine, Jr. Am. Med. Assoc., 1940, cxiv, 1605–1611.

4. WYRENS, RAYMOND J.: The clinical toxicity of sulfanilamide and its related drugs, Nebraska State Med. Jr., 1941, xxvi, 220–223.

5. HOGAN, BARTHOLOMEW W., and McNAMARA, PHILIP J.: Psychosis precipitated by sulfanilamide, U. S. Naval Med. Bull., 1938, xxxvi, 60.

6. YOUNG, ROBERT E. S.: Psychosis due to sulfanilamide, Ohio State Med. Jr., 1939, iii, 847.

7. PEARSON, MANUEL M., and BRUNSTINE, M. DAVID: Psychosis precipitated by sulfanilamide—report of two cases, Internat. Clin., 1939, iii, New Series II, 246.

8. OTTENBERG, REUBEN: Clinical experiences with sulfanilamide therapy with special references to toxic effects, New York State Jr. Med., 1939, xxxix, 418–430.

9. BLOCK, W. H.: Psychosis precipitated by sulfanilamide, Jr. Med. Assoc. Alabama, 1940, ix, 339.

10. TOLLER, RUDOLPH B.: Psychosis due to sulphanilamide, California and West. Med., 1940, liii, 266–267.

11. WAUGH, J. R.: Psychosis during administration of sulfanilamide, Am. Jr. Syph., Gonor., and Ven. Dis., 1941, xxv, 504–507.

12. CURRENT COMMENT: Impaired judgment from sulfanilamide, Jr. Am. Med. Assoc., 1941, cxvi, 2279–2280.

CASE REPORTS

THROMBOCYTOPENIC PURPURA COMPLICATING ACUTE CATARRHAL JAUNDICE; REPORT OF A CASE, REVIEW OF THE LITERATURE, AND REVIEW OF 48 CASES OF PURPURA AT UNIVERSITY HOSPITAL *

By THEODORE E. WOODWARD, M.D., *Baltimore, Maryland*

THE purpose of this paper is (1) to report a case of thrombocytopenic purpura complicating acute catarrhal jaundice; (2) to present a review of all of the cases of purpura at the University Hospital with reference to jaundice; and (3) to report a review of the literature on this clinical picture.

CASE REPORT

The patient, a 14 year old white boy, was admitted July 27, 1939 from the Rosewood State Training School. Little is known of the past history other than that he was illegitimate, and both parents were deceased. His early years were spent in a county home, the latter at the above mentioned training institution. Past illnesses included several attacks of tonsillitis, and jaundice with fever in 1938. The latter attack was short in duration and was not associated with purpura.

The present illness began seven days prior to admission with headache, anorexia, and general malaise. The patient stated that he did have a little fever and that his stools were light in color, with dark colored urine. (A report from the institution revealed that he had bile pigments and bile salts in the urine.) No medication was used other than a saline purgative and a proprietary capsule consisting of bile salts. Icterus was noticed on the third day of the illness, accompanied by intense itching. On the following day the patient noticed small, red, non-elevated areas on the chest and abdomen which soon became generalized, covering the entire body. Stools at this time were dark in color and on two occasions black. Bleeding from the gums began two days prior to, and continued up to admission. There was slight nausea at this time but no vomiting, and other than the bleeding and itching the patient felt quite well. No history could be obtained of eating mushrooms, taking toxic drugs, tick bites, or other possible causes.

Physical Examination: The patient was a well developed white boy, alert and oriented, and deeply jaundiced. The body was completely covered with myriads of hemorrhagic, non-elevated areas varying in size from a pinhead to a quarter. None faded on pressure. The mucous membrane of gums, soft palate, and pharynx was also studded with purpuric spots. The sclerae were deeply icteric, with minute hemorrhages present. The fundi were normal with the exception of two small petechiae on the right side. Nose: There were petechiae on the mucous membrane. Mouth: There was free bleeding from the lips and gum margin. The mucous membrane was studded everywhere with petechiae. The tonsils were quite large and chronically infected. There were a few large glands in both anterior cervical groups which were not tender. Heart and lungs were essentially negative. The liver extended three fingers' breadth below the costal margin and to the fourth rib anteriorly. The edge was sharp but not tender. The tip of the spleen was easily palpated.

TABLE I

Summary of Laboratory Examinations of Case Reported

Date	Platelets	Ict. Index	Van. d. Bergh	Bleeding T.	Clotting T.	Prothrom. T.	Galact. Tol.	Hippuric Ac.	Bromsulf. T.	Bl. Fibrinogen	Bl. Amino Acid	N.P.N.	Bl. Sugar	Bl. Ca. and P	Urine Bile	Urine Urobilin	Stool Benzid.	Stool Guaiac	Bile	Tourniquet T.	Bl. Culture	Fragility T.	R.B.C.	W.B.C.
July 27	39,070	106	9.3	12¼'	13'	12''						27	96	9.4 / 4.4	+	+	+++	+++	+	6		0	4.4	5,100
28	38,200														+	+	+++	+++					4.5	
29	39,310																+++				0		4.6	
30	55,930																++						4.3	
31	57,070																						4.4	
Aug. 1	85,080						5.4 gm.								+	0			Tr.	97			4.1	
2	115,360	172	19												+	0							4.1	
3								1.04 gm.		.27 gm. %	6.6 mg. %	23			+	+								
4	106,310	116	10	5¼'	11½'	12'									+	0	+	0	+	4			4.1	
5															Tr.	0	++	Tr.	0					
6															Tr.	0	++	Tr.	+				4.1	
7	197,760	80	6												0	0	0	0	+					
8																							4.1	
9	385,400	64	4.3												0	0		0						
10																								
11																								
12		43	3														0	0						
13																								
14																								
15		48	3	2¼'														0						
16	569,800				2'										0	0							3.7	
17																								
18																								
19																								
20																								
21		25	2.3												0	0								
22																								
23	688,500	23	1.9						0														4.3	8,300 Retic. 4.4%
24																								
25																								
26																								
27															0	0								
28																								
29																								
30																								
31																								
Sept. 1																								
2							1.6 gm.																	

Extremities: The legs and arms were completely covered with petechiae varying in size. There was no cyanosis nor clubbing of the nails. Platelet count was 39,070. The urine contained bile pigments and bile salts with urobilin. No cystine or leucine crystals were noted. Tourniquet test revealed six additional petechiae. Stool showed occult blood and trace of bile.

Clinical Course: There was slight fever, the maximum temperature observed being 99.8° F. The tonsils were injected, and on the fourth day one of the right cervical lymph nodes became enlarged and tender. Under treatment which included administration of placental extract, calcium lactate in large doses, cevitamic acid and two transfusions, each of 100 c.c. of citrated blood, the bleeding ceased after three days. The platelet count rose more slowly. Jaundice continued to be intense until the seventh day after admission, with clay colored stools, then it gradually faded. The liver and spleen diminished in size. The patient was discharged September 2, 1939, apparently well except for a faint tract of jaundice.

Laboratory Examinations: Data of significance are summarized in table 1. There was evidence of impaired liver function, as shown by the high icterus index, strongly positive direct van den Bergh reaction, high excretion of galactose and low excretion of hippuric acid. There was, however, no increase in prothrombin time and fibrinogen was normal.

Biliary drainage on the sixth day yielded only a small quantity of "A" bile, which showed E. coli in culture. A guinea pig inoculated with urine on the ninth day did not show Leptospira icterohemorrhagiae.

TABLE II

Summary of 48 Cases of Purpura from the Records of the University Hospital

Diagnosis	Number of Cases	Platelets Below 60,000	Jaundice	Died	Splenectomy	Splenomeg.
Thrombocytopenic purpura....	26	9	0	4	3	8
Acute yellow atrophy.........	1		1	1	0	0
Symptomatic purpura........	11	0	2	3	0	0
Arthritic purpura...........	10	0	0	0	0	0

Cases of Purpura at the University Hospital. A total of 48 cases of purpura of all types was found in the records of the University Hospital. Of these, 26 cases, or 54 per cent, were placed in the idiopathic thrombocytopenic group. The remainder were equally distributed between the arthritic and symptomatic forms, the former group including the cases of purpura simplex and anaphylactoid purpura of the Schönlein-Henoch type. These are summarized in table 2.

None of the cases of thrombocytopenic purpura showed any clinical evidence of jaundice. One, however, had a delayed direct van den Bergh reaction with 2.4 mg. per cent of bilirubin in the serum. In this particular case the spleen was palpated and complete recovery followed splenectomy. The platelets rose postoperatively from 59,000 to 470,000 in three days. No evidence of liver damage was noted. Included in this group are three cases of purpura believed due to a deficiency of vitamin C, which were treated effectively with large doses of cevitamic acid. In one case the spleen was irradiated following which there was a slow rise in the platelet count from 160,000 to 260,000 in five days. Three cases developed as a complication of pregnancy, all of which made a favorable

recovery. In none of these did the platelet count become lower than 180,000. Three cases in the hemorrhagic group came to splenectomy, following which there was a prompt rise of platelets and recovery. Hepatic function tests were not done because there was no clinical evidence of liver damage.

The one case of acute yellow atrophy is considered because of the purpura which developed terminally. In this patient there was widespread liver destruction, evidenced by an icteric index of 257, a direct prompt van den Bergh reaction with 20.3 mg. per cent of bilirubin, and a blood amino acid of 16 mg. per cent. Urinary bile pigments were 4 plus. Unfortunately, blood platelets, bleeding and clotting times were not recorded. Necropsy revealed a widespread central necrosis with a few scattered petechial hemorrhages.

One case in the symptomatic group is significant in that the purpura developed during what was believed to be an acute catarrhal jaundice. Liver and spleen were not palpated, bile pigments were not present in the urine, but urobilin was 4 plus. The purpura consisted of a few pin point hemorrhages on the legs and buttocks and the platelet count was never lower than 384,000. Van den Bergh reaction was prompt direct, with 2.8 mg. per cent of bilirubin. Bleeding, clotting, and clot retraction times were all within normal limits. The patient recovered completely.

The arthritic group contributes nothing from the point of view of platelet or liver deficiency.

The problem of principal interest presented by this case is the association of disease of the liver and spleen with platelet deficiency. Did the liver damage per se cause a destruction of the platelets, was the spleen responsible, or can the cause be sought in dysfunction of the entire reticulo-endothelial system? There was obvious liver damage present in the patient, evidenced by hepatomegaly, jaundice of a rather severe nature, and a marked discrepancy between the various liver function tests. Rosenberg[1] stated that in 10 cases of acute catarrhal jaundice there appeared to be no relationship between the degree of icterus in different patients and the amount of galactose excreted. He found that an extensive and very diffuse process is essential for an abnormal galactose output. This is based on the actual observation of liver sections of a severe case of intrahepatic jaundice, which had been studied clinically. An excretion of over three grams of galactose in the urine is generally accepted as abnormal.

The presence of large amounts of urobilin is further evidence of hepatic derangement since this pigment is normally converted into bilirubin by the liver and excreted as such in the intestinal tract. Normally the kidneys may excrete a small amount. In Rosenberg's 10 cases urobilin was present in the urine at one time or other. Darries[2] concluded that the presence of urobilin in the urine indicates intrahepatic jaundice, whereas its absence indicates an obstructive jaundice. This is in accord with present clinical conceptions.

Regarding the formed blood elements and their relationship to liver damage, several things are in evidence. It is generally found that blood fibrinogen is increased in cases of jaundice. Burke[3] reported an increase in values of blood fibrinogen in four cases of catarrhal jaundice. In addition he reported an increase of fibrinogen in 79 per cent of 43 jaundiced cases. Of these cases 20 gave evidence of hemorrhagic tendencies demonstrated by purpura, epistaxis, etc. Platelet studies in these cases were not recorded.

Platelet deficiency has been attributed to liver disease. Weil [4] reviewed 20 cases of liver disease, chosen arbitrarily. Eleven of these 20 cases showed platelet counts below 150,000. This was in association with decreased retractility of the clot and prolongation of the bleeding time. He made no explanation for the deficiency. King [5] reported an appreciable decrease of platelets in 20 per cent of 100 cases of portal cirrhosis. In this particular series he found jaundice in 50 per cent of the cases, a rather high figure.

Prothrombin, an essential element in the clotting process, was formerly believed to be entirely derived from a breakdown of blood platelets (Barker [6]). Recent studies by Quick [7] and others indicate that prothrombin deficiency is due to injury of the liver, in most cases. In the present case the finding of a relatively normal amount of prothrombin in the face of the marked platelet deficiency would not be in harmony with the former belief. Quick states that prothrombin deficiency is responsible for hemorrhage, yet the majority of jaundiced cases do not bleed. This he attributes to a wide margin of safety in the prothrombin content of the blood, in that 80 per cent of this factor may be depleted before the hemorrhagic tendency manifests itself. He attributes the depletion to the absence of bile salts and acids in the intestinal tract causing a faulty absorption of vitamin K. Repeated studies by many observers, including Carr,[8] Quick,[7] King,[5] Abrami,[9] reveal that blood fibrin, fibrinogen and calcium are usually normal in jaundice.

In the present case we must assume that rather widespread liver injury was present. There was gross enlargement of the organ, deep jaundice, and abnormal amounts of urobilin in the urine. Galactose was excreted in abnormal amounts, and the hippuric acid excretion was diminished. Bleeding and clotting times were decidedly prolonged above normal, but blood fibrinogen was normal. Clinically the case may be regarded as one of catarrhal jaundice, with anorexia, abdominal discomfort, slight fever, bilirubinemia and bilirubinuria.

It does not seem likely, however, that the liver injury per se was responsible for the thrombocytopenia. Abrami [9] stated that the liver is not the determining factor in the production of purpura. His view was based on the fact that in experimental lesions of the liver, prolonged bleeding time, thrombocytopenia and nonretractility of the clot do not occur. Capillary fragility, he does admit, is seen in severe icterus as in the advanced stage of all cirrhoses.

In this case there was also splenomegaly and some generalized lymphadenopathy, affecting chiefly the cervical glands. There is considerable evidence that the spleen plays an active part in the removal of platelets from the circulation. Splenectomy is the most effective form of therapy in essential thrombocytopenic purpura and is usually followed by a prompt rapid increase of platelets.

Of the few cases at the University Hospital all showed an appreciable rise averaging 400,000 in three days. Evans,[11] in a study of 11 cases following splenectomy, found a marked temporary rise and a slow fall to normal. In his cases of hemorrhagic purpura the peak was reached in eight days with a fall to normal in 10 to 20 days. In his cases of splenic anemia the maximum was reached in 15 days with a considerable decline in two to three weeks, and a normal count was reached after 100 days. As the platelet count rises, the bleeding time and retractility time of the clot shorten, with formation of a firmer and more effective clot. The degree to which coagulation is stimulated is not pro-

portional to the increase in platelets above a normal level, but it is substantial and may even cause death as a result of mesenteric or portal thrombosis.

The mechanism by which the spleen exerts this function is not known. Torrioli [10] isolated from the spleen and other organs a substance which injured the megakaryocytes of the bone marrow and indirectly caused a shortage of platelets. The organs varied in their content of this substance in the following order: thymus, spleen, lung, lymph nodes, liver, heart and skeletal muscle. This degree of activity is proportional to their content of reticulo-endothelial tissue.

Brill [12] reported a case of chronic hemolytic icterus with a marked thrombocytopenia showing improvement after splenectomy. He believed the spleen was primarily at fault, but suggested that the disease involves the whole reticuloendothelial system, bone marrow, liver and spleen.

On the basis of the foregoing evidence we may assume a diffuse derangement of the reticuloendothelial tissue, including the spleen, liver and lymph glands. The process certainly was initiated by an apparently typical catarrhal jaundice. Treatment probably had little effect in bringing about the complete recovery.

A search of the literature revealed very few reported cases showing thrombocytopenic purpura in association with catarrhal jaundice. One practically identical case was reported by Alt and Swank.[13] This patient also recovered.

Loeper and de Seze [14] reported the occurrence of purpuric spots on the legs and body in cases of secondary cancer of the liver. The bleeding time and clotting time were prolonged and clot retraction was delayed. They state that purpura may occur in any type of liver disease if liver function is seriously impaired.

Stone and Bunim [15] reported a case of a 27 year old pregnant woman who developed a peculiar purpuric eruption on the face after delivery. Jaundice appeared seven weeks later, and terminated in acute yellow atrophy. The relationship of the purpura to the jaundice seems questionable.

Jones and Minot [16] reported 26 cases of catarrhal jaundice, none of which showed purpura.

A review of the cases of purpura at the University Hospital revealed one mild case of purpura associated with catarrhal jaundice. The hemorrhagic tendency was slight and unassociated with platelet deficiency or liver damage. In the case of acute yellow atrophy which terminated fatally there were purpuric hemorrhages noted at autopsy.

SUMMARY

1. A case is reported of thrombocytopenic purpura associated with catarrhal jaundice and impaired liver function.

2. It seems probable that the thrombocytopenia was not due directly to impaired liver function but to an associated disturbance of the reticuloendothelial tissue.

3. A search of the literature revealed only one similar case.

BIBLIOGRAPHY

1. ROSENBERG, D. H.: Galactose and urobilinogen tests in differential diagnosis of obstructive and intrahepatic jaundice, ANN. INT. MED., 1934, viii, 60–71.

2. DARRIES, D. H.: Diagnosis of hepatic disorders, Lancet, 1927, i, 380–384.

3. Burke, C. F., and Weir, J. F.: Hemorrhagic tendency in jaundice, Jr. Lab. and Clin. Med., 1933, xviii, 657–667.

4. Weil, P. E.: La diminution des hematoblastes dans les affections hepatiques, Compt.-rend. Soc. de biol., 1922, lxxxvii, 143–144.

5. King, R. B.: Blood picture in portal cirrhosis, New England Jr. Med., 1929, cc, 482–484.

6. Barker, L. F.: Splenic anemia, etc., Med. Clin. N. Am., 1930, xiv, 57–70.

7. Quick, A. J.: Nature of bleeding in jaundice, Jr. Am. Med. Assoc., 1938, cx, 1658–1662.

8. Carr, J. L., and Foote, F. S.: Progressive obstructive jaundice, Arch. Surg., 1934, xxix, 275–296.

9. Abrami, P.: Le purpura des hepatiques, Ann. de méd., 1935, xxxvii, 71–79.

10. Torrioli, M., and Puddu, V.: Recent studies of the pathogenesis of Werlhof's disease, Jr. Am. Med. Assoc., 1938, cxi, 1455–1456.

11. Evans, W. H.: Blood changes after splenectomy in splenic anemia, purpura hemorrhagica, and acholuric jaundice, etc., Jr. Path. and Bact., 1928, xxxi, 815–831.

12. Brill, N. E.: Chronic hemolytic icterus, Med. Clin. N. Am., 1924, viii, 153–174.

13. Alt, Howard L., and Swank, Roy L.: Catarrhal jaundice associated with thrombocytopenic purpura, Ann. Int. Med., 1937, x, 1049–1054.

14. Loeper, M., and De Seze, S.: Le purpura d'alarme dans le cancer secondaire du foie, Progrès méd., 1930, vii, 282–287.

15. Stone, M. L., and Bunim, J. J.: Cutaneous hemorrhage during puerperium with later development of acute yellow atrophy, Am. Jr. Obst. and Gynec., 1936, xxxi, 1015–1019.

16. Jones, C. M., and Minot, G. R.: Catarrhal jaundice, etc., Boston Med. and Surg. Jr., 1923, clxxxix, 531–551.

A CASE REPORT OF CUTANEOUS LEPROSY WITH A BRIEF DISCUSSION OF THE CLASSIFICATION, TREATMENT, AND EPIDEMIOLOGICAL PORTENT *

By Felix R. Park, M.D., F.A.C.P., J. Roderick Kitchell, M.D., F.A.C.P., and Samuel G. Shepherd, M.D., F.A.C.P., Philadelphia, Pennsylvania

M. B., a 67 year old Russian Jew, was first admitted to the hospital May 26, 1937, with a simple fracture of the neck of the left femur following a fall. At this time he gave a history of dyspnea on exertion for many years, and a chronic cough for at least a year. The physical examination showed a short, thick-set, elderly man whose face was somewhat leonine and whose eyebrows were thin in the lateral thirds. The pupillary reflexes were normal. Both inferior turbinates were hypertrophied, especially the left. The pharynx was injected and the breath was fetid. His dental hygiene was poor and the tonsils were small and embedded. Many coarse moist râles were present at the lung bases. The heart was not enlarged and no murmurs or arrhythmias were present. The patient was seen by the ear, nose and throat consultant because of his chronic sinusitis and by the dentist for mouth hygiene. The rhinologic examination disclosed pus in the middle fossa of the left nostril, and evidences of chronic pansinusitis for which conservative treatment was recommended. A roentgenogram of the chest demonstrated a generalized bronchovascular thickening, and in the absence of any more definite roentgenological findings early bronchiectasis was considered. A non-hemolytic streptococcus and Staphylococcus albus were found by culture of the sputum. Except for negative Wassermann and Kahn reactions the remainder of the laboratory findings were insignificant as far as this report is concerned, and the patient was dismissed as cured of the fractured femur on August 10, 1937.

Subsequently he was attended in the Medical and Surgical Out Patient Clinics irregularly and was referred early to the Ear, Nose and Throat Clinic since his nasal disease steadily progressed. The turbinates ulcerated and the nasal septum developed a lesion which eventually perforated. Two biopsies were taken from this lesion because of the suspicion of neoplasm, and the reports were as follows: July 1, 1938 —subacute granulation tissue. December 30, 1938—chronic hypertrophic rhinitis.

The patient complained of pain in both arms and legs and, when the administration of salicylates was ineffectual, he was referred to the clinic for peripheral vascular diseases. There a provisional diagnosis of atypical Buerger's disease was made, but various recognized treatments for this condition failed to produce any therapeutic results. At this time, mostly on account of the typical facies, but especially since this was coexistent with lesions, it was decided that leprosy was most probably the correct diagnosis. Therefore, the patient was hospitalized on the medical ward for study May 28, 1939.

On this occasion examination revealed an elderly man obviously suffering pain on motion of the extremities. The face had a "lion-like" appearance owing to the nodular thickening of the skin of the nose, forehead, cheeks, and lobes of the ears. The mucous membranes of the nose and throat were congested and the pharynx was granular. Fetor oris was marked and there were numerous small ulcers in the roof of the mouth which extended also to the nares, and a perforation of the anterior portion of the nasal septum was present. The skin over the entire body was dry and there was a peculiar brownish color of the hands and feet. Many red spots about ½ cm. in diameter were seen over the body, as well as many scratch marks. A few coarse basal râles were found in the lungs, but the heart examination was normal. No masses or tender areas were felt within the abdomen, although there was a left indirect inguinal hernia. The hands and feet were quite tender to pressure, and the posterior tibial and dorsalis pedis arteries were not palpable on either side. The reflexes were hypoactive throughout.

The diagnoses were pediculosis corporis, left indirect inguinal hernia, avitaminosis and chronic upper respiratory disease. Leprosy and peripheral vascular disease were tentatively diagnosed. Slides were made by scraping the lesions of the mouth and nose with a dull scalpel, and these when stained with the acid-fast technic were found to be loaded with lepra bacilli. A biopsy was then made from a nodule in the skin of the face and this was reported by Dr. Philip Custer as follows:

"*Gross Description:* Specimen consists of small pieces of firm, white, blood-stained tissue.

"*Microscopic Description:* The nodule is covered by epidermis and is formed by inflammatory tissue of chronic granulomatous nature, with fibroblastic proliferation being rather markedly in evidence. In some areas a foamy quality to certain of the macrophages is evident. The smears from the cut surface of the first specimen show many acid-fast organisms which conform morphologically to the bacilli of leprosy. Similar organisms are recovered after centrifugation of a sample of blood.

"*Pathologic Diagnosis:* Leprosy. B. leprae recovered by deRivas method from blood."

As soon as the diagnosis was established the Public Health authorities were notified and it was discovered that this man's wife died of leprosy eight years previously. He had temporarily moved to another city and had avoided surveillance by the local Department of Public Health. Since his return, and without reporting the fact to us, he had attended various clinics in many local institutions, both before and concurrently with his visits to our clinics. In his peregrinations about the city for six years or more a great many physicians examined him in the various dispensaries and in the period of hospitalization for an unrelated condition, and all completely overlooked the diagnosis.

This sporadic case of leprosy has been of special interest inasmuch as failure to evaluate all the physical findings was responsible for delaying the diagnosis. During this time members of the community were exposed, for the patient mingled with others and even visited public baths regularly.

DISCUSSION

The cardinal points for a diagnosis of leprosy are obtainable from standard textbooks of medicine, but the classification was revised at the Manila conference of the Leonard Wood Memorial for the Eradication of Leprosy, January 1931. The term "mixed type" was discontinued since the disease may be disseminated throughout the body and evidence of both the cutaneous and neural involvement is usually and probably always present. It was decided that the cases should be grouped upon the basis of the predominant lesions found, either neural or cutaneous. Provision was made for the "secondary neural cases," those in which the condition is resultant to irreversible damage to the nervous system but in which evidence of active disease processes can no longer be obtained by clinical methods.

At this same conference the term "cured" was discouraged and "arrested" was substituted to designate those cases in which there has been no positive clinical microscopic evidence of disease for a period of two years or more.

In the treatment of leprosy each case is managed individually and no single specific drug is employed. Particular attention is given to associated disorders that may determine the course of the disease and its therapeutic response. Various physiotherapeutic and chemical measures are used depending on the indication. The complications require appropriate medical, surgical, or orthopedic treatment as indicated. Preparations of oils of the chaulmoogra group have been most widely used. More recently Douglas Collier reports that diphtheria toxoid (formol) is now employed with encouraging results. It is possible that in time this may provide a method of treatment whereby the patient may remain at home, and it might be of great aid as a prophylaxis.

The presentation of this case of leprosy is especially timely since our soldiers are now fighting where this disease is more prevalent than in any other part of the world, and no doubt exposure will result with symptoms developing in some of the troops returning from this theater of war. Because of these facts our knowledge of the disease must be more thorough and the possibility of its occurrence must always be kept in mind.

It may be stated that the problem of leprosy will be interesting from the epidemiological standpoint, since we will be able to evaluate the incidence among those exposed and determine whether the impression that there is a familial tendency is tenable, and therefore whether segregation of those who are victims from members of their families should prevail. We will also be able to see whether racial resistance exists among the new exposures and whether the colored race is more resistant to the infection than the white race. Hitherto it has been difficult to determine the incubation period since the time of exposure was not known in many instances. However, if this disease develops in some of the returning soldiers a more definite impression may be gained as to the period required after exposure before the onset with its initial signs and symptoms. Likewise, it will be determined more conclusively whether a prolonged

exposure to the disease or single exposures to the more infectious skin types are responsible for the transmission.

BIBLIOGRAPHY

1. HOPKINS, RALPH, and DENNEY, OSWALD E.: A statistical study of seven hundred cases in The National Leprosarium, Jr. Am. Med. Assoc., 1929, xcii, 191–198.
2. Leonard Wood Memorial for Eradication of Leprosy: Report of Conference at Manila, Jr. Am. Med. Assoc., 1931, xcvii, 53–54.
3. COLLIER, D. R.: The use of diathermy in leprosy: a preliminary report, Thai Sci. Bull., 1940, ii, 109–116.
4. COLLIER, D. R., and McKEAN, J. H.: The use of diphtheria antitoxin and toxoid in leprosy: a preliminary report, Thai Sci. Bull., 1940, ii, 117–125.
5. COLLIER, DOUGLAS: New treatment for lepers, Mod. Hosp., 1941, lvii, 49.

ACINAR CELL CARCINOMA OF PANCREAS: REPORT OF CASE IN WHICH FUNCTION OF CARCINOMATOUS CELLS WAS SUSPECTED *

By MANDRED W. COMFORT, M.D., F.A.C.P., HUGH R. BUTT, M.D., F.A.C.P., ARCHIE H. BAGGENSTOSS, M.D., ARNOLD E. OSTERBERG, M.D., and JAMES T. PRIESTLEY, M.D., *Rochester, Minnesota*

WE are reporting a case of acinar cell carcinoma of the pancreas in which values for enzymatic activity in the serum were many times greater than those usually encountered in cases of carcinoma of the pancreas. These values were so high that we entertained the possibility that functioning of the acinar cell carcinoma contributed to their height.

CASE REPORT

A man, aged 49 years, a Polish printer, was admitted to the Mayo Clinic September 9, 1940. During the preceding 10 years he had had an ulcerous type of dyspepsia which had been periodic, occurring in attacks of one to two weeks in length, once or twice yearly. Three months before his admission, an apparently typical attack of ulcerous dyspepsia had begun and had become by far the worst he had ever experienced; for the first time the pain had extended to his back and awakened him at night. The pain, which was relieved by food or soda, was still a major complaint at the time of his registration at the clinic. Two months before admission diarrhea had begun; the stools numbered two to four daily, were bulky, malodorous and light in color and floated on the water. Five weeks before admission, pain in both lower quadrants of the abdomen had begun. Three weeks before admission, the patient had noted swelling of the abdomen. At that time some anorexia developed but hardly enough to account for the loss of 40 pounds (18.1 kg.) which had taken place in the last three months.

On admission the patient did not appear to be acutely ill, but there was evidence of much loss of weight. Icterus was not present. Collateral venous circulation in the abdominal wall was not developed visibly. Palpation did not reveal the liver or the spleen or distention of the gall-bladder. There was slight ascites, but edema, peripheral or dependent, was not present.

The value for hemoglobin was 13.1 gm. per 100 c.c., the erythrocytes numbered 4,600,000 and the leukocytes 10,500 per cubic millimeter of blood. The percentages of the various kinds of leukocytes were as follows: lymphocytes 18.5, monocytes 5, neutrophiles 74.5, eosinophiles 1 and basophiles 1. Morphologic study of the erythrocytes disclosed that they were slightly enlarged but that marked macrocytosis was not present. Routine urinalysis revealed albumin, graded 2; the results otherwise were negative. The results of routine flocculation tests for syphilis were negative as were roentgenograms of the thorax, the colon and the terminal portion of the ileum. One hour after the ingestion of eight arrowroot cookies and two glasses of water, 65 c.c. of gastric contents were recovered by tube; analysis of the contents disclosed that total acidity was 82, and free hydrochloric acid 76 (Töpfer's method). Roentgenographic examination of the stomach revealed a duodenal ulcer. The concentration of urea in the blood was 14 mg. per 100 c.c.; that of cholesterol in the plasma 181 mg. per 100 c.c., and that of bilirubin in the serum 1.1 mg. per 100 c.c.; the van den Bergh reaction was direct. The Quick prothrombin time was 25 seconds. The bromsulfalein test of hepatic function disclosed a dye retention of grade 3. The glucose tolerance test revealed a flat type of curve. Quantitative analysis of a single stool showed that 59.3 per cent (dry weight) was fat. Proctoscopic examination disclosed only internal and external hemorrhoids. The values for lipase and amylase in the serum were extremely high; they were respectively, 9.7 c.c. of twentieth-normal solution of sodium hydroxide for each cubic centimeter of serum and 4,000 units for each 1 c.c. of serum (method of Somogyi[1]) (figure 1).
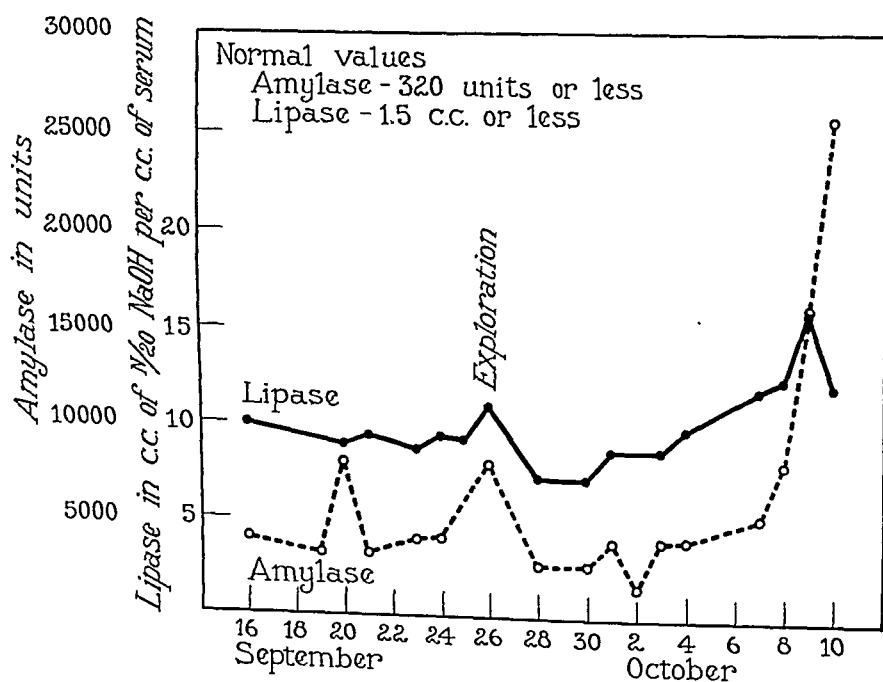
Fig. 1. Values for activity of lipase and amylase in the serum.

The tentative diagnosis was of penetrating duodenal ulcer with secondary pancreatitis. However, the marked loss of weight, the ascites, the steatorrhea and the extremely high values for enzymes in the serum were such unusual features that hospitalization of the patient for observation and preoperative preparation was proposed and carried out. A strict regimen for ulcer was instituted, but in spite of this measure, the pain continued. A low intake of fat controlled the diarrhea. The values

for lipoids in the plasma were low: cholesterol 151, cholesterol esters 111, lecithin 192, fatty acids 291 and total lipoids 442 mg. per 100 c.c. The values for lipase in the serum varied during the period from September 17 to September 25, inclusive, from 8.7 to 9.4 c.c. of twentieth-normal solution of sodium hydroxide for each cubic centimeter of serum and for amylase in serum from 3,200 to 8,000 units for each cubic centimeter of serum (figure 1). It became clear that the pain was not now of the ulcerous type and that the duodenal ulcer was not responsible for the patient's illness. The progressive character of the illness, the marked loss of weight, the steatorrhea and the sustained high levels of enzymatic activity heretofore observed only in neoplastic disease of the pancreas led [2] to diagnosis of carcinoma of the pancreas, and because of the exceedingly high level of enzymatic activity in the serum, the presence of a functioning acinar cell carcinoma was suspected.

An exploratory operation was performed September 26, 1940 through a midline incision. When the peritoneal cavity was opened, brownish ascitic fluid was disclosed, a large amount of which was aspirated and preserved for study. There were a number of metastatic nodules in the liver; a portion of one of these nodules was removed for microscopic examination, which revealed adenocarcinoma of grade 2. The pancreas had a rounded edge and was markedly indurated and thickened. This change was present throughout the gland, and seemed to be most marked in the head of the pancreas. All of the peritoneal tissues appeared to be congested as though they had been subjected to the action of some irritant. Small individual blood vessels were apparent over the entire peritoneum. It appeared likely that the primary lesion was in the pancreas, but inasmuch as metastasis had occurred already, extensive exploration did not seem justifiable, and the wound accordingly was closed.

A culture of the ascitic fluid did not reveal organisms. Values for lipase and amylase in the ascitic fluid were respectively 127 c.c. of twentieth-normal solution of sodium hydroxide per cubic centimeter and between 50,000 and 75,000 units of amylase per cubic centimeter.

The patient's convalescence was uneventful. His pain persisted. The diarrhea was controlled fairly well with a low intake of fat. The ascites reformed partially. The values for lipase and amylase in the serum remained extremely high, reaching levels not observed by us previously in either benign or malignant neoplastic disease of the pancreas. The values for activity of lipase and amylase were respectively 15.8 c.c. of twentieth-normal solution of sodium hydroxide per cubic centimeter of serum and 25,600 units per cubic centimeter of serum. A dextrose tolerance curve was again of the flat type. The patient was dismissed October 24, 1940.

Through the coöperation of the patient's family physician, we were informed of the development of jaundice, and of the painful and progressively downward course. The patient died February 27, 1941. With the coöperation of the patient's physician, the opportunity was given to examine the liver, pancreas, duodenum and stomach five days after death. In this interval, the tissues were preserved in dry ice.

Pathologic Examination of Specimen Obtained at Necropsy. A large, firm, nodular mass which was approximately 5 cm. in diameter was found in the head of the pancreas. On the cut surface the tumor was grayish white with numerous yellowish areas scattered over it (figure 2), it was very hard, and had a granular appearance. The mass had compressed and partially obstructed the common bile duct and the duct of Wirsung. Both of these ducts were greatly dilated proximal to the lesion.

On the anterior aspect of the body of the pancreas was a cyst-like structure which was approximately 4 cm. in length and 2.5 cm. in depth and in width (figure 2). It was densely adherent to the posterior wall of the stomach. Its contents consisted of greenish yellow fluid and crystals of ice. The wall was formed of fibrous tissue lined by yellowish gray, necrotic tissue. The splenic artery traversed the cavity and a por-

tion of the thrombosed splenic vein formed part of the wall. The wall of the splenic vein in this region appeared to be necrotic. No connection could be found between the dilated and tortuous duct of Wirsung and the cyst-like cavity. In the region of this structure there were several yellowish, softened areas.

The tail of the pancreas was somewhat fibrotic but was otherwise normal. The regional lymph nodes were enlarged and firm and on the cut surface appeared grayish white, homogeneous and granular.

The liver weighed 4,350 gm., and the normal contour was distorted by grayish nodular masses of varying sizes. The largest mass was present in the right lobe and measured 20 by 15 by 12 cm. The cut surfaces of these masses were grayish white and granular and had the appearance of metastatic carcinoma. The intervening hepatic parenchyma was deep green.
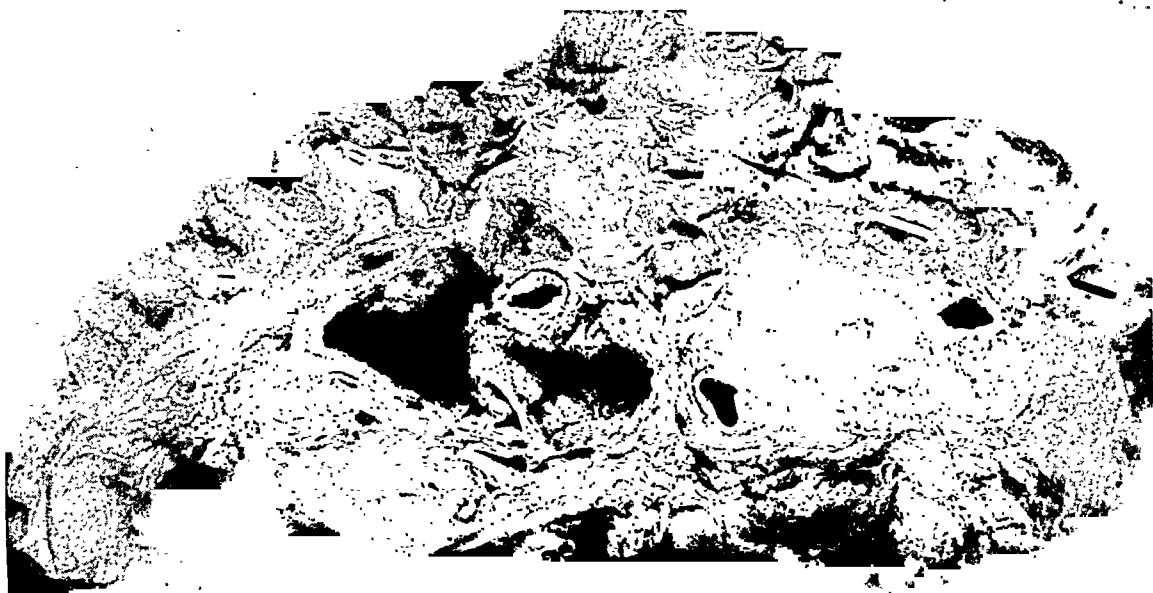
FIG. 2. Carcinoma of head of pancreas with probe in common bile duct. Note pseudocyst in body of pancreas with splenic artery transversing it.

The extrahepatic and intrahepatic bile ducts and the gall-bladder were dilated. The gall-bladder contained about 100 c.c. of bile and the wall appeared normal.

The stomach appeared normal but on the posterior wall of the duodenum there was a shallow chronic duodenal ulcer which measured 0.8 cm. in diameter.

Histologic Examination. Sections taken from the mass in the head of the pancreas revealed a cellular adenocarcinoma which was graded 2 (on the basis of 1 to 4, in which 1 is the least and 4 the most malignant). There was definite formation of acini by the neoplastic cells and the appearance was consistent with that of a carcinoma arising from the acinar tissue of the pancreas (figure 3a). The cells forming the acini were roughly pyramidal in shape. The cytoplasm of these cells was acidophilic except for a narrow zone in the basilar portion which was faintly basophilic with hematoxylin and eosin stains. The cytoplasm was vacuolated but zymogen granules could not be identified. Although the nuclei were hyperchromatic, mitotic figures were rare. Mucin could not be demonstrated by appropriate stains. In many regions of the carcinoma there was no evidence of tendency to form acini; the cells were present in solid masses separated by wide bands of fibrous connective tissue. The neoplastic cells in these regions generally were elongated in appearance. In some regions there was definite evidence of postmortem autolysis. The carcinoma had invaded the nor-

FIG. 3. Pancreas. *a*, Acinar carcinoma of head of pancreas. Note formation of acini (hematoxylin and eosin, ×160). *b*, Portion of wall of pseudocyst (hematoxylin and eosin, ×100).

mal parenchyma and resulted in destruction of the adjoining acinar tissue and the islands of Langerhans. In sections taken from the duct of Wirsung in the head of the pancreas, the neoplasm was found to have invaded the wall and almost completely obstructed the lumen.

The wall of the cyst-like structure was found to consist of fibrous, hyalinized, connective tissue without any evidence of an epithelial lining (figure 3b). On the inner surface of the wall there were patches of fibrin and necrotic debris. Included in the fibrous tissue wall there were macrophages containing lipoids and numerous collections of lymphocytes, many of which were perivascular. Deposits of hemosiderin and hematoidin also were present. Deep in the wall neoplastic cells were found in the perineural lymphatic structures. The surrounding parenchyma showed evidence of degeneration together with an interlobular fibrosis.

In addition to the large pseudocyst there were several smaller cyst-like structures which contained granular debris, fibrin and hematogenous pigments surrounded by a wall of fibrous connective tissue.

In the tail of the pancreas there was atrophy of the parenchyma with interlobular and intralobular fibrosis. Carcinoma could not be found in this portion of the pancreas and the ducts were dilated moderately.

In sections of the tumors in the liver, a cellular adenocarcinoma was discovered which appeared identical with the pancreatic carcinoma. The surrounding hepatic cells appeared compressed and atrophied and the sinusoids were dilated.

The following anatomic diagnoses were made: (1) Carcinoma of the head of the pancreas (acinar type), (2) metastasis to the liver and lymph nodes, (3) obstruction of the common bile duct with jaundice (clinically), (4) obstruction and dilatation of the duct of Wirsung with atrophy of the tail of the pancreas, (5) pseudocyst of the pancreas (residual of acute pancreatic necrosis) and (6) ascites.

Chemical Examination of Material Obtained at Necropsy. The activity of amylase was determined by the method of Somogyi and that of lipase by the method of Cherry and Crandall as modified by Comfort and Osterberg.[3]

Amylase was not demonstrated in either hepatic tissue or metastatic carcinoma of the liver. Values for amylase in pancreatic tissue removed from the region of the head of the pancreas, in fluid removed from the cyst, and in the ascitic fluid were respectively 400 units per gram, 1066 units per cubic centimeter and 520 units per cubic centimeter.

Values for lipase in hepatic tissue, metastatic carcinoma of the liver, and tissue from the head of the pancreas were respectively 7.0 c.c., 6.0 c.c., and 8.0 c.c. of twentieth-normal solution of sodium hydroxide per gram. Values for lipase in fluid removed from the pancreatic cyst and in the ascitic fluid were respectively 23.3 c.c. and 1.0 c.c. of twentieth-normal solution of sodium hydroxide per cubic centimeter of fluid. It is worthy of note that the values for amylase and lipase in the ascitic fluid removed at necropsy were much less than those in the ascitic fluid removed at operation.

COMMENT

From the pathologic findings it seems reasonable to attribute the regions of necrosis and the formation of the pseudocysts in the body of the pancreas to attacks of acute pancreatic necrosis secondary to neoplastic obstruction of the duct of Wirsung. In retrospect the more severe attacks of pain may well have been the result of such attacks of acute pancreatic necrosis. At the time of necropsy the duodenal ulcer did not appear to have been very active.

The nature of the carcinoma does not appear questionable. It was clearly of the acinar cell type. The source of the large amounts of amylase and lipase in the blood and in the ascitic fluid is the chief point of interest.

Several explanations may be advanced for the high values for enzymatic activity in this case. First, the high values were due to obstruction of the pancreatic ducts by the carcinoma. Experimentally, in dogs, ligation of the pancreatic ducts is followed by a rise in values for enzymatic activity in the serum. The obstruction increases the intraductal pressure, ruptures the small radicles of the pancreatic ducts, permits pancreatic juice to enter the lymphatics and ultimately the blood stream. The values return to normal in from 10 to 14 days, presumably because the obstructive pancreatitis subsides and secretion is suppressed. In man, elevated values for lipolytic activity of the serum have been found in 40.5 per cent and for amylolytic activity of serum in 8 to 22 per cent of cases of carcinoma of the pancreas. We may assume that obstruction of the pancreatic ducts by carcinoma of the pancreas produces the elevated values for enzymatic activity in the serum in a manner similar to that in experimental ligation of the ducts and that elevated values are not present in all cases because the carcinoma does not obstruct the ducts in all cases and because obstruction of the duct finally destroys the acinar structures which are the source of enzymatic activity, permitting the values to return to normal. Second, in this case, pancreatitis was responsible for the high values for activity of enzymes in the serum. Pancreatitis had undoubtedly been present at some time during the course of the disease. The inflammatory pseudocysts, we believe, were the residue of pancreatic necrosis. The pancreatitis was the result of obstruction and might have been responsible at one time for the elevation in the values for enzymatic activity in the serum along with the obstruction of the ducts. Third, absorption through the walls of the inflammatory cysts and of the blood vessels traversing the cavity of the cyst contributed to the high values for enzymatic activity in the serum. Although this factor must be considered, it may be pointed out that the cysts are not known to have been present at the time the high enzymatic activity was found in the serum and the ascitic fluid. At least, such cysts were not found at the time of surgical exploration.

The values for enzymatic activity in the serum in this case were higher than those previously seen in other cases of carcinoma of the pancreas. In Comfort and Osterberg's series of cases of carcinoma of the pancreas, an occasional value of 6 or 7 c.c. of twentieth-normal sodium hydroxide per 1 c.c. of serum for lipolytic activity has been observed, but usually the values have been in the range of 2 to 4 c.c. of twentieth-normal sodium hydroxide per cubic centimeter of serum, while the values for amylase as a rule have been less than 1,000 units. Values for lipolytic activity of 9 to 10 c.c. of twentieth-normal sodium hydroxide per 1 c.c. of serum and for amylase of 4,000 to 8,000 units per cubic centimeter of serum were obtained consistently in this case; the values were so much higher than those previously encountered that we wondered whether obstruction of the duct by carcinoma and secondary pancreatitis constituted adequate explanation for the high values for enzymatic activity in the serum and whether some other factor was contributing to the high values. Later, when values for lipolytic activity reached 15.8 c.c. of twentieth-normal sodium hydroxide per 1 c.c. of serum and for amylase 25,800 units per cubic centimeter of serum, we were ready to believe that some other factor was contributing to the exceedingly high values. It occurred to us that a functioning acinar cell carcinoma of the pancreas might be the additional factor. Demonstration that high values persisted throughout life would have furnished strong evidence that the carcinoma of the

pancreas was functioning, because values elevated by obstruction of the pancreatic duct should have returned to normal as atrophy of the acinar structures of the pancreas progressed and probably would have returned to normal long before the patient's death. Unfortunately, we could not carry out such determinations.

Although examination of the material obtained at necropsy showed that the carcinoma was of the acinar cell type, chemical examination of the metastatic nodules in the liver for amylolytic and lipolytic content did not furnish the evidence that we sought, to show that the carcinoma was functioning; namely, that metastatic carcinoma contained enzymes in quantities greater than the parenchyma of the liver in which the nodules were embedded.

We do not believe that functioning of the acinar cell carcinoma should be discarded as an accessory cause of the high values in this case because of the absence of chemical proof. It is possible that the content of enzymes in the tissues examined was altered profoundly during the five days which elapsed between the death of the patient and examination of the tissues. It is not unlikely that acinar cell carcinomata of the pancreas do function and produce high values for enzymatic activity in the serum. In support of this probability it may be pointed out that many neoplasms carry on some of the functions of their parent cells. Especially is this true of certain tumors arising from the endocrine glands such as the suprarenal glands, the ovaries and the pituitary body, as well as carcinoma of the islands of Langerhans. Carcinoma arising from glandular organs is also known to function, as evidenced, for example, by the mucin and pseudomucin produced in numerous adenocarcinomata, the production of bile by hepatomata and of colloid by carcinomata of the thyroid gland. Ewing [4] stated that chemical studies support the belief that some cancerous tissues are capable of carrying on cellular function, as shown by the high content and qualities of lipoids in hypernephroma and the considerable content of iodine in thyroid carcinoma. He demonstrated that as a rule functional activities diminish with increasing anaplasia and that original overactivity then is succeeded by complete failure, as in the pigment-free metastatic lesions of melanoma.

SUMMARY

In this case of acinar cell carcinoma of the pancreas the values for lipolytic activity and particularly for amylolytic activity in the serum and the ascitic fluid were exceedingly high. Various explanations of the high values have been considered. It is possible that the high values were owing entirely to obstruction of the pancreatic ducts, to the obstructive pancreatitis or to absorption of enzymes from the pancreas and the pseudocyst. The values for enzymes were so much higher, however, than in any other case of carcinoma of the pancreas observed by us, that an explanation other than these was sought. The possibility that the high values were due to functioning of the acinar cell carcinoma was examined and, although the data have been too incomplete to warrant the conclusion that the carcinoma was functioning, the possibility is an attractive one that deserves consideration in future cases of carcinoma of the pancreas with high values for amylolytic and lipolytic activity in the serum. The case has been reported to call attention to the possibility that acinar cell carcinomata of the pancreas may function and may be responsible for high values for enzymatic activity in the serum.

BIBLIOGRAPHY

1. SOMOGYI, MICHAEL: Micromethods for the estimation of diastase, Jr. Biol. Chem., 1938, cxxv, 399.
2. COMFORT, M. W., and OSTERBERG, A. E.: The value of determination of the concentration of serum amylase and serum lipase in the diagnosis of disease of the pancreas, Proc. Staff Meet. Mayo Clin., 1940, xv, 427.
3. COMFORT, M. W., and OSTERBERG, A. E.: Serum amylase and serum lipase in the diagnosis of disease of the pancreas, Med. Clin. N. Am., 1940, xxiv, 1137.
4. EWING, JAMES: Neoplastic diseases, Fourth edition, 1940, W. B. Saunders Company, Philadelphia, p. 38.

EDITORIAL

FAILURE OF THE VENOPRESSOR MECHANISM AS A FACTOR IN THE DEVELOPMENT OF SHOCK

THE importance of the rôle of the venopressor mechanism in maintaining the circulation has become generally known in large part through the work of Henderson and his associates. Henderson[1] has recently summarized his conceptions of this mechanism and the significance of its failure in the production of shock.

Maintenance of a normal circulation (i.e., a normal minute-volume output by the heart) depends not merely upon an effectively functioning myocardium but also upon the delivery through the veins to the right side of the heart of a quantity of blood sufficient to fill the cavities. There had long been difficulty in explaining satisfactorily the mechanical factors which bring about the return flow of an adequate volume of blood through the veins. The valves in the veins serve an important function in determining the direction of flow and preventing any reflux back into the tissues. Manifestly they do not contribute any positive force to the circulation. There is also a small positive pressure in the venous end of the capillaries and venules which, in conjunction with an intrathoracic pressure which is slightly below the atmospheric pressure, propels blood toward the heart. This vis-a-tergo, however, is relatively slight and seemed scarcely an adequate explanation, particularly in conditions in which the blood flow is accelerated.

Henderson has shown that an important contributing force is provided by the contractions of the skeletal muscles. As has been pointed out by Krogh, there is an abundant anastomosing network of arterioles, capillaries and venules interspersed between the muscle fibers. The veins are abundantly provided with valves which permit blood to flow only toward the heart. These vessels are filled with blood during periods of muscular relaxation, but during contraction of the muscle fibers, the increase in girth of the fibers, associated with their shortening, exerts pressure on the vascular network and vigorously propels blood onward into the veins. This action is compared to that of a peripheral or "booster" pump, which powerfully supplements the relatively feeble vis-a-tergo supplied by the cardiac contractions and the arterial pressure. This mechanism evidently must play a vital part in securing adequate return flow to the heart during periods of intense muscular activity when the rate of blood flow may be increased even to five times the resting rate.

Even in periods of muscular rest, however, Henderson believes this same force is operating and is equally important in maintaining a normal circulation. During health there is never complete relaxation of the muscles. Even when the body is as completely at rest as possible, the muscles are con-

[1] HENDERSON, Y.: Tonus and the venopressor mechanism: the clinical physiology of a major mode of death, Medicine, 1943, xxii, 223–249.

tinuously in a state of partial contraction or "tonus." This tonus is maintained by stimuli coming through the motor nerves from the motor nuclei of the spinal cord and bulb. During rest only a few of the muscle bundles are contracting at a given moment, but the successive contraction and relaxation of the muscle bundles exert a similar booster action that differs only quantitatively from that accompanying voluntary contraction.

As one proof of these contractions Henderson has cited the presence of action currents in electromyograms of resting muscles, and the increase in amplitude of these currents when measures are taken to increase the muscle tonus.

Henderson has devised a simple clinical procedure for determining the effectiveness of the venopressor mechanism and the adequacy of the venous blood return. The subject is placed, head down, on a table tilted at an angle of 45°. The arm is held vertically, and the height of the column of blood in the distended veins is measured. In patients with grave illness he was able to demonstrate a progressive lowering of this blood column as death approached. He thinks this is a more valuable indication of the need of plasma injections in shock than arterial blood pressure or estimations of venous pressure in the recumbent position.

The degree of muscle tonus and its accompanying "booster" action depends upon the "tone" of the spinal motor centers. This, in turn, is affected by a multitude of factors, mental, physical and chemical. It is much affected by respiration and by the concentration of carbon dioxide in the blood. Inhalation of carbon dioxide increases the tonus: Hyperventilation and pumping out of carbon dioxide (acapnea), on the other hand, lower tonus, reduce the effect of the booster pumps, and slow the return flow of blood to the heart, with resulting circulatory failure if it is too long continued.

Any serious impairment of the general health may reduce the tone, which Henderson speaks of as an "index of vitality." It is much reduced in the physical depression which accompanies serious acute or chronic illness, increasingly so as death is approached. Henderson believes that the "peripheral circulatory failure" which is the immediate cause of death in such conditions is not dependent upon loss of vasomotor tone, but upon inadequate return flow of blood to the heart which results from failure of this venopressor mechanism.

The pain and shock following physical injury or operation also diminish the "normal tonic function" of the motor centers. Henderson believes that the circulatory failure which accompanies shock may also be explained by a failure of the venopressor mechanism rather than by relaxation of the peripheral vessels following exhaustion of the vasomotor center. "When the tonic influence of the motor centers fails, the skeletal musculature becomes flaccid. Because of this flaccidity, the intramuscular pressure falls; the capillary pumps cease to operate; and the venous return to the heart diminishes until it becomes insufficient to allow the heart to maintain the

arterial blood stream and pressure. So the first, or circulatory stage of shock develops."

As the rate of blood flow falls, the oxygen requirement of the tissues is not met, and tissue asphyxia results. Seepage of the plasma from the capillaries then sets in, with progressive decrease in blood volume, further slowing of the circulation, and finally an abrupt fall in arterial blood pressure.

In animals intravenous administration of large amounts of fluid at this stage will restore the blood pressure and pulse amplitude, indicating that the circulatory collapse was not due to failure of the heart or vasomotor system. Saline solution will restore the circulation temporarily, but plasma is far more efficient.

Henderson believes that leakage of plasma from the vessels is due more to tissue asphyxia than to loss of plasma protein. This is based on plasmapheresis experiments, in which severe protein depletion was produced without any loss of fluid from the vessels provided the red cells were replaced and anoxemia avoided. He thinks the late manifestations of posthemorrhagic shock are also a result of tissue asphyxia, and strongly advocates transfusions of whole blood rather than merely plasma in such cases. This is also in accordance with the recommendations of the British War Office.

Henderson points out that this conception of shock eliminates the old puzzling question, "when the circulation fails without a hemorrhage, where has the blood gone?" It is not necessary to assume that the blood is pooled in the splanchnic vessels or in any other unusual location. "It simply slows and then stops circulating." It is to be found "essentially where it was when flowing . . . and the asphyxial tissues absorb the plasma."

Henderson emphasizes the rôle of carbon dioxide in controlling this venopressor mechanism. Both at rest and during muscular exertion "the amount of carbon dioxide produced in the tissues and carried by the blood to the central nervous system determines the tonic influences of the motor centers upon the muscles, and so the activity of their booster pumps and the volume of the venous return." It "determines alike the volume of the air breathed, the volume of the venous return and thereby the volume of blood circulated." Vasomotor reactions, on the other hand, are mainly concerned with adjustment of the arterial pressure and the distribution of the blood in the arterial system.

Without attempting an extensive discussion of this controversial question, it must be pointed out that Henderson's views as a whole have not been generally accepted. Many investigators feel that he has overemphasized the rôle of hyperpnea and acapnea in the production of shock, and has underestimated the importance of loss of fluid from the vessels. His work, in any case, is highly stimulating, and he has made many contributions of major importance to this subject. There can be little doubt that the venopressor mechanism is an important factor in maintaining and regulating the rate of blood flow.

REVIEW

Practical Survey of Chemistry and Metabolism of the Skin. By MORRIS MARKOWITZ,
M.D. 196 pages; 13.5 × 20.5 cm. The Blakiston Company, Philadelphia. 1942.
Price, $3.50.

To the reviewer's knowledge, this monograph is the only essay of its kind in pub-
lication and covers the subject of chemistry and metabolism of the skin succinctly and
quite fully within the limits of the space available.

The author should not permit himself the liberty of dealing in probabilities as,
for instance, on page 23, where he states "The probability is that it (hyperglycemia)
is a hepato-pancreatic disturbance or a metabolic disorder." He also states on page
21, "Predisposition to certain dermatoses may also be caused by carbohydrate intake
by producing an excessive secretion of fat in the skin and carbohydrate excretion in
the sweat." To make such a statement is begging the question. There are several
more similar statements as on page 47, "Vitamin C is probably a catalyzing enzyme."
And on page 71, "moist compresses and fomentations may produce spread of infec-
tion."

Aside from this and several other similar statements, the book is worth careful
reading. I would hesitate, however, to accept this statement: "Dermatologically
it (panthothenic acid) is of interest as an anti-gray hair factor and antidermatitic."

H. M. R.

BOOKS RECEIVED

Books received during September are acknowledge in the following section. As
far as practicable, those of special interest will be selected for review later, but it is
not possible to discuss all of them.

The Ear, Nose and Throat in the Services. By R. SCOTT STEVENSON, M.D., F.R.C.S.,
Ed.; Major R. A. M. C. 116 pages; 17 × 11 cm. 1943. Oxford University
Press, New York. Price, $1.50.

Microscopic Technique in Biology and Medicine. By E. V. COWDRY, Professor of
Anatomy, Washington University. 206 pages; 23.5 × 16 cm. 1943. The Wil-
liams and Wilkins Company, Baltimore. Price, $4.00.

Nervousness, Indigestion and Pain. By WALTER C. ALVAREZ, M.D. 488 pages;
24.5 × 16.5 cm. 1943. Paul B. Hoeber, Inc., New York. Price, $5.00.

War Endocrinology. By JAMES H. HUTTON, M.D. 363 pages; 23.5 × 16 cm. 1943.
The Wayside Press, Chicago.

Synopsis of Tropical Medicine. By SIR PHILIP MANSON-BAHR, C.M.G., D.S.O.,
M.D., F.R.C.P. 224 pages; 19 × 12.5 cm. 1943. Williams and Wilkins Com-
pany, Baltimore. Price, $2.50.

*Primeras Reuniones Extraordinarias de la Asociación de Médicos del Hospital
Durand.* Two volumes. 1428 pages; 23.5 × 16.5 cm. 1942. Caporaletti Hnos.,
Buenos Aires.

*La Prueba Intradérmica de Giroud en la infección tifoexantemática. Nuestra Ex-
periencia Personal. Técnicas y Posibilidades de su Aplicación.* By G. CLAVERO
and F. PÉREZ GALLARDO. 65 pages; 24 × 17 cm. 1942. (Publicaciones de la
Revista de Sanidad e Higiene Publica.) Imprenta de J. Cosano. Madrid.

Investigación del virus tifoexantemático en las ratas de España. By G. CLAVERO and
F. PÉREZ GALLARDO. 25 pages; 24 × 17 cm. 1943. (Publicaciones de la Re-
vista de Sanidad e Higiene Publica.) Imprenta de J. Cosano. Madrid.

Tifus Exantemático. Etiología, Clínica, Profilaxis. By G. CLAVERO and F. PÉREZ
GALLARDO. 166 pages; 25 × 17.5 cm. 1941. Gráficas Afrodisio Aguado, S.A.,
Madrid.

COLLEGE NEWS NOTES

Additional A. C. P. Members in the Armed Forces

Already published in preceding issues of this journal were the names of 1,482 Fellows and Associates of the College on active military duty. Herewith are reported the names of 7 additional members, bringing the grand total to 1,489.

James E. Bovaird   Warren M. Gilbert
James H. Danglade   Lester D. Watson
Herbert K. Ensworth   John C. White
                    Bertrand O. Woods

New Life Members of the College

The following Fellows of the American College of Physicians have subscribed to Life Membership, and their initiation fees and Life Membership subscriptions have been added to the permanent Endowment Fund of the College:

Dr. H. Sheridan Baketel, Jersey City, N. J.
Dr. Constantine P. Faller, Harrisburg, Pa.
Dr. Harold G. Trimble, Oakland, Calif.

Gifts to the College Library

The following gifts to the College Library of Publications by Members are gratefully acknowledged:

Dr. Truman G. Schnabel, F.A.C.P., Philadelphia, Pa.—"The Scope of 1942," University of Pennsylvania School of Medicine Yearbook.

Reprints

John E. Garcia (Associate), Lieutenant, (MRC), U. S. Army—1 reprint;
Bernard A. Goldman (Associate), Lieutenant, (MRC), U. S. Army—1 reprint;
Dr. Arthur J. Logie, F.A.C.P., Miami, Fla.—1 reprint;
R. Bruce Logue (Associate), Major, (MRC), U. S. Army—1 reprint;
Dr. Bernard J. McCloskey (Associate), Johnstown, Pa.—1 reprint;
Dr. Frederick W. Mulsow, F.A.C.P., Cedar Rapids, Iowa—1 reprint.

Third Annual Schering Award Competition

The third nation-wide competition for the Schering Award is now open. Three major prizes of a total value of $1,000 will be awarded to undergraduate medical students who submit the best critical dissertations on the subject, "Hormones and Cancer." As in previous years, the Judges for the Schering Award will include outstanding American investigators in the fields of endocrinology, medicine and chemistry.

The Schering Award was established by the Schering Corporation in 1941, for the purpose of encouraging a wider interest in current endocrinological developments among undergraduate medical students. The competition is sponsored and administered by the Association of Internes and Medical Students, and participation is limited to undergraduate medical students in the United States and Canada. It is noted that all manuscripts must be submitted no later than January 15, 1944. Communications should be addressed to "The Interne," 7 East 42nd Street, New York 17, N. Y.

The fifth painting in the famed "Pioneers of American Medicine" series sponsored by John Wyeth & Brother, and entitled "The Father of American Pharmacy," was unveiled at ceremonies November 5 during National Pharmacy Week in Philadelphia. The painting depicts William Procter (1817–1872) studying a formula for the standardization of drugs while at work with an assistant in his laboratory. The principal speaker was Dr. Ivor Griffith, Ph.M., Sc.D., F.R.S.A., President of the American Pharmaceutical Association and of the Philadelphia College of Pharmacy and Science.

Dr. Charles F. McKhann, F.A.C.P., Professor of Pediatrics and Communicable Diseases at the University of Michigan Medical School, has resigned to accept a position as Assistant to the President of Parke, Davis and Company of Detroit. Dr. McKhann will devote his time entirely to the scientific activities of the company. He assumed his duties October 15.

Since 1930, he has conducted and directed research on communicable diseases, immunology, renal diseases, nutritional diseases, and on certain phases of toxicology. He developed and introduced immune globulin and has contributed to the development of several other products.

The Medical Society of the State of Pennsylvania conducted its 93rd Annual Session in Philadelphia, October 5–7, under the Presidency of Dr. Augustus S. Kech, F.A.C.P., of Altoona. Among the guest speakers was Dr. Wallace M. Yater, F.A.C.P., Washington, D.C., whose subject was "Selection and Interpretation of Laboratory Procedures."

The Kansas City Annual Fall Clinical Conference was held in Kansas City, October 4–6, 1943, under the Presidency of Dr. James E. Stowers. Many distinguished authorities from various parts of the country appeared on the program, including Dr. Paul D. White, F.A.C.P., Boston, Dr. E. H. Rynearson, F.A.C.P., Rochester, Minn., Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Mich., and Dr. Harrison F. Flippin, F.A.C.P., Philadelphia.

One evening was given over to a panel discussion of "Navigating the Medical Future," which included discussions of the Wagner-Murray Senate Bill No. 1161, which would impose compulsory health insurance; improvements in the standards of medical education and the influences that may jeopardize these standards in the regimentation of medical students; the group hospitalization plan of voluntary prepayment for medical services that is in operation in the Jackson and Wyandotte County Medical Societies; methods now used in many Kansas counties for payment of medical services for indigent and low income groups; the American philosophy of private enterprise as the best means of promoting a prosperous peace and maintaining the integrity of American life and happiness; and the program for medical care favored by the American Federation of Labor.

Dr. Nathan S. Davis, F.A.C.P., Chicago, Assistant Professor of Medicine at Northwestern University Medical School, was the recipient of the Distinguished Service Award of the Mississippi Valley Medical Society for 1943. The award, consisting of a gold medal and certificate, was presented to Dr. Davis by the Society's President, ·Dr. Edward M. Myers, at Quincy, Ill., September 30, during the 9th Annual Meeting of that Society. The citation reads, "A high type of physician, an able clinician, a very accurate investigator and last but not least, a writer of syndicated medical advice for the public. While he descends from an illustrious family in medicine, he has carved his own niche in the profession."

Dr. M. Fernan-Nunez, F.A.C.P., Professor of Pathology in the Marquette University Medical School, Milwaukee, toured South Dakota from September 19 to 26, giving lectures on tropical diseases to medical groups in Aberdeen, Huron, Sioux Falls, Pierre, Rapid City and Fort Meade. Soldiers and sailors returning from tropical service, and tourists coming back from vacations in the southern states and Mexico, are bringing into northern latitudes an increasing amount of exotic diseases, especially malaria. Dr. Fernan-Nunez' trip was sponsored as a joint project of the South Dakota State Board of Health and the United States Public Health Service to bring the latest developments in the field of tropical medicine to the medical profession of that state.

Dr. M. Fernan-Nunez also lectured to the medical officers of Camp McCoy, Wis., September 6, on "Malaria," as a member of the national faculty of War-Time Graduate Medical Meetings.

THE MEAD JOHNSON VITAMIN B COMPLEX AWARD

Nominations are solicited for the 1944 award of $1,000 established by Mead Johnson and Company to promote researches dealing with the B complex vitamins. The recipient of this award will be chosen by a committee of judges of the American Institute of Nutrition. The award will be given to the laboratory (nonclinical) or clinical research worker in the United States or Canada who, in the opinion of the judges, has published during the previous calendar year January 1 to December 31 the most meritorious scientific report dealing with the field of the B complex vitamins. While the award will be given primarily for publication of specific papers, the judges are given considerable latitude in the exercise of their function. If in their judgment circumstances and justice so dictate, it may be recommended that the prize be divided between two or more persons. It may also be recommended that the award be made to a worker for valuable contributions over an extended period but not necessarily representative of a given year. Membership in the American Institute of Nutrition is not a requisite of eligibility for the award.

To be considered by the committee of judges, nominations for this award for work published in 1943 must be received by the secretary, Arthur H. Smith, Ph.D., Wayne University College of Medicine, Detroit, by Jan. 10, 1944. The nominations should be accompanied by such data relative to the nominee and his research as will facilitate the task of the committee of judges in its consideration of the nomination.

Major R. Bruce Logue (Associate), MRC, U. S. Army, Chief of Cardiovascular Section of Lawson General Hospital, Atlanta, Ga., gave the A.O.A. address at Emory University Medical School on September 17, 1943. The title of the address was "Neurocirculatory Asthenia."

Dr. James E. Paullin, Atlanta, Ga., President, A.C.P., addressed the 37th Annual Meeting of the Southern Medical Association held in Cincinnati, November 16–18.

Dr. Joseph J. Combs, F.A.C.P., Raleigh, N. C., was elected Treasurer of the North Carolina Tuberculosis Association at a recent meeting.

Dr. Jerome E. Andes, F.A.C.P., former instructor in the West Virginia University School of Medicine and more recently Medical Director of the Hercules Powder Company, Lawrenceville, Kan., has returned to Morgantown to become Director of the Student Health Center at the University.

Dr. Newton G. Evans, F.A.C.P., Dean of the College of Medical Evangelists, Los Angeles, has been elected President of the Alumni Research Foundation of that institution, which has been incorporated under the laws of California for the primary purpose of stimulating research.

Captain Henry L. Dollard, F.A.C.P., (MC), U. S. Navy, Senior Medical Officer of the Ninth Naval District, Great Lakes, Ill., presided over a panel discussion on "War Medicine and Surgery" conducted in connection with the Eleventh Annual Assembly of the Omaha Mid-West Clinical Society, October 25–29.

Among guest speakers on the program were Dr. Harold G. Wolff, F.A.C.P., New York, N. Y., "Headache Mechanisms"; Dr. Sara M. Jordan, F.A.C.P., Boston, "Functional Diseases and the War"; and Dr. Tom Spies, F.A.C.P., Birmingham, Ala., "Detailed Methods of Diagnosis and Therapy in Acute Nutritive Failure."

Dr. Wesley W. Spink, F.A.C.P., Minneapolis, is Secretary of the American Society for Clinical Investigation.

Dr. Roger I. Lee, F.A.C.P., Boston, addressed the second Profession-Industry Follow-Up on the National Conference on Planning for War and Postwar Medical Services at the Waldorf-Astoria Hotel in New York City, October 4, his title being "Medicine's Position and Policy."

Under the Presidency of Dr. Waller S. Leathers, F.A.C.P., Dean of Vanderbilt University School of Medicine, Nashville, Tenn., the 54th Annual Meeting of the Association of American Medical Colleges was held in Cleveland, October 25–27. Among speakers on the program were Brigadier General George F. Lull, F.A.C.P., U. S. Army, "The Army Specialized Training Program"; Commander Bartholomew W. Hogan, F.A.C.P., U. S. Navy, "The Navy V 12 Program"; Dr. Willard C. Rappelye, F.A.C.P., New York City, "Postwar Planning for Medical Education"; Dr. Joseph T. Wearn, F.A.C.P., Cleveland, "Present Methods of Medical Teaching"; Dr. Carl J. Wiggers, F.A.C.P., Cleveland, "Correlation of Physiology Instruction with War Problems."

Dr. Russell M. Wilder, F.A.C.P., has resigned as Chief of the Civilian Food Requirements Branch of the Food Distribution Administration, Washington, and will resume his activities at the Mayo Clinic, Rochester, Minn.

Brigadier General Eugen G. Reinartz, F.A.C.P., of the U. S. Army, addressed the 15th Annual Meeting of the Aero Medical Association of the United States at Cincinnati, October 26–27.

The University of Illinois recently accepted a grant of $25,000 a year for three years from the Upjohn Company, Kalamazoo, Mich., for the study of penicillin in their Biochemistry Department at Urbana.

Major General James C. McGee, F.A.C.P., formerly Surgeon General of the U. S. Army, recently addressed the faculty and students of New York University College of Medicine on the subject of military medicine, with particular reference to tropical diseases.

Brigadier General Charles C. Hillman, F.A.C.P., U. S. Army, addressed the Medical Society of Virginia at Roanoke, October 25–27, on "Medical Operations in the Pacific Theaters."

Dr. Abraham H. Aaron, F.A.C.P., Buffalo, N. Y., was a speaker on the program devoted to the art and science of therapeutics at the 93rd Annual Session of the Medical Society of the State of Pennsylvania, Philadelphia, October 5-7.

Dr. Theodore G. Klumpp, F.A.C.P., who is now President of the Winthrop Chemical Company, has been elected a member of the Academia de Ciencias Medicas, Fisicas y Naturales de la Habana, Cuba.

Among guest speakers and lecturers who participated in giving the Alumni Association Refresher Course of the Medical College of the State of South Carolina, Charleston, November 3-4, were Dr. George W. Thorn, F.A.C.P., Boston, "Physiologic Considerations in the Treatment of Nephritis"; Dr. Harrison F. Flippin, F.A.C.P., Philadelphia, "The Uses and Abuses of the Sulfonamides"; Dr. Charles C. Wolferth, F.A.C.P., Philadelphia, "Differential Diagnosis of the Anginal Syndrome"; Dr. Virgil P. Sydenstricker, F.A.C.P., Augusta, "Deficiency Diseases."

Dr. Oscar Lotz, F.A.C.P., Milwaukee, and Dr. John H. Skavlem, F.A.C.P., Cincinnati, have been elected Vice President and Secretary-Treasurer, respectively, of the Mississippi Valley Trudeau Society.

Dr. Felix Hurtado, F.A.C.P., Havana, Cuba, was a guest speaker on the program of the 72nd Annual Meeting of the American Public Health Association, New York City, October 11-14.

Dr. Walter A. Bastedo, F.A.C.P., New York City, was Chairman of a panel discussion on "Use of Sulfonamides in Gastrointestinal Diseases" under the auspices of the Sixteenth Graduate Fortnight of The New York Academy of Medicine, October 19.

The War-Time Graduate Medical Meetings Committee has announced the rapid growth and expansion of the programs being given at Army and Navy hospitals and installations all over the United States and, in some instances, in Canada. These meetings are under the joint auspices of the American College of Physicians, the American Medical Association and the American College of Surgeons.

Under the Chairmanship of Dr. James J. Waring, F.A.C.P., a three-day course of meetings was given at the Fitzsimmons General Hospital and at the University of Colorado and the Colorado General Hospital, Denver, September 30-October 2.

Under the Chairmanship of Dr. E. L. Henderson, Louisville, and his Committee consisting of Dr. Chauncey W. Dowden, F.A.C.P., Louisville, and Dr. H. H. Shoulders, Nashville, a course was conducted at the Dyersburg (Tenn.) Army Air Base and the Kennedy General Hospital, Memphis, Tenn., September 20, 21, 22, 23, 24 and 25.

Under the Chairmanship of Dr. Carl Mulky, F.A.C.P., Albuquerque, and with his Committee consisting of Dr. Fred G. Holmes, F.A.C.P., Phoenix, and Dr. L. B. Cohenour, Albuquerque, a course was conducted October 13-15 at Kirtland Field, Albuquerque, and on October 18-20 at the Davis-Monthan Field, Tucson.

NORTH CAROLINA A. C. P. REGIONAL MEETING

Under the Chairmanship of Dr. Paul F. Whitaker, F.A.C.P., Kinston, College Governor for North Carolina, a state meeting of the College was held at the Bowman Gray School of Medicine at Winston-Salem, October 29. Dr. Wingate M. Johnson,

F.A.C.P., Winston-Salem, was Chairman of the Program Committee. Not only were members of the College invited to attend, but likewise all medical officers of the armed forces in the territory.. The program was as follows:

AFTERNOON SESSION—2:00 p.m.

Amphitheater

Bowman Gray School of Medicine

"The Typhus Fever Problem in North Carolina."
>   T. W. BAKER, M.D., F.A.C.P., and JAMES M. ALEXANDER, M.D., (Associate, A.C.P.), Charlotte, N. C.

"Coronary Occlusion."
>   WILLIAM B. DEWAR, M.D., F.A.C.P., Raleigh, N. C.

"Changing Phases in the Treatment of Tuberculosis."
>   PAUL H. RINGER, M.D., F.A.C.P., Asheville, N. C.

"Clinico-Pathological Conference."
>   ARTHUR GROLLMAN (by invitation) and ROBERT P. MOREHEAD, M.D., (Associate, A.C.P.), Winston-Salem, N. C.

EVENING PROGRAM

Robert E. Lee Hotel

7:00 Dinner (Informal)

Guest Speaker

WILLIAM B. CASTLE, M.D., F.A.C.P., Boston, Mass.
"As They Were: Colored Pictures of Australia and the East in 1938."

Remarks

CHARLES H. COCKE, M.D., F.A.C.P., First Vice President, A.C.P.
PAUL F. WHITAKER, M.D., F.A.C.P., Governor for North Carolina.

OBITUARIES

DR. HARRO WOLTMANN, F.A.C.P.

Dr. Harro Woltmann of Mansfield, Ohio, died December 27, 1942, of tuberculosis. He was born in Chicago, Ill., October 15, 1882, graduated from the University of Michigan Medical School in 1905, and interned at the University of Michigan Hospital. He was a resident at the Lakeside Hospital, Cleveland, 1905–06. During his earlier years, he did postgraduate work in Boston, New York, Philadelphia and Los Angeles. For many years Dr. Woltmann was Chief of Staff of the Mansfield General Hospital and was actively interested in the work of the Richland County Tuberculosis and Health Association, serving as Chairman of the Program Committee and as a member of its Executive Committee.

He had been a Fellow of the American College of Physicians since 1928, having at that time been sponsored by the late Drs. Aldred Scott Warthin, John Phillips and Frank Smithies.

DR. GUY LEARTUS CONNOR, F.A.C.P.

Dr. Guy Leartus Connor of Detroit, Michigan, died at Fort Lauderdale, Florida, April 19, 1943, of cerebral hemorrhage. He was born at Detroit, October 10, 1874, graduated from Williams College (A.B., 1897), and received his medical degree from Johns Hopkins University School of Medicine in 1901.

For many years he was a member of the staffs of the Children's Hospital of Michigan, Harper Hospital and St. Mary's Hospital, all of Detroit. Formerly he was Assistant Clinical Professor of Neurology, Psychiatry and Preventive Medicine at the Detroit College of Medicine, and at one time Medical Director of the Detroit Board of Education.

Dr. Connor had been a member, and in 1928 President, of the Federation of State Medical Boards. From 1917 to 1929, he was a member of the Michigan State Board of Registration in Medicine, and served as its Secretary from 1924 to 1929. He was a former President of the Michigan State Medical Society, and served some time as the Managing Editor of its journal. He also served for several years as a member of the House of Delegates of the American Medical Association.

Dr. Connor was among the early Fellows (1917) of the American College of Physicians, and maintained an active, interested part in its activities the remainder of his life.

COLONEL EDGAR FREMONT HAINES, (MC), U.S.A.

Colonel Edgar Fremont Haines, (MC), U.S.A., a Fellow of the College, died July 22, 1943, and received a military funeral at the Arlington National Cemetery, Arlington, Va.

Colonel Haines was born at Fairhaven, Mass., March 10, 1883. He graduated from the Boston University School of Medicine in 1906 and immediately thereafter entered the Medical Corps of the U. S. Army, and served continuously for thirty-three years. During his tour of duty, Colonel Haines served in the Philippine Islands, in Mexico and in China. His decorations included the Mexican and the Expeditionary medals. In the course of his career he studied at the Army Medical Field Service School at Carlisle Barracks, Carlisle, Pa., and for a time was Professor of Military Medicine at Boston University School of Medicine. He traveled extensively throughout this Country, and his foreign duty came in 1910 with the 13th Infantry in Davao, P. I. He was later transferred to China, where he served during the Revolution in 1913. He was the Attending Surgeon at the Army Base in Boston for six years and the Surgeon of the Army War College in Washington, D. C., for four years. His last assignment was to direct the activation of the Station Hospital at Fort Dix, N. J.

Colonel Haines was a member of the Association of Military Surgeons, the American Medical Association and the Military Order of Carabao. He had been a Fellow of the American College of Physicians since 1932. He is survived by his wife, Nathalie, of Brookline, Mass., by a daughter, Mrs. Donald F. Taylor, wife of a Coast Artillery Captain, and two brothers, Dr. G. A. Haines, of Everett, Mass., and Mr. Herbert Haines, of Lowell, Mass.

THIOCYANATE GOITER IN MAN *

By RULON W. RAWSON,† S. HERTZ, and J. H. MEANS, F.A.C.P.,
Boston, Massachusetts

THAT a definite relationship exists between iodine deficiency and many non-toxic goiters is well established. Indeed endemic goiter is usually, and perhaps too readily, accepted as being due to iodine deficiency. Experimentally, thyroid hyperplasia has been produced in various laboratory animals by many goitrogenic agents other than iodine deficient diets. Astwood, et al.[1] in a recent report, referred to extensive literature on a variety of goitrogens.

Some of the most interesting studies in goitrogenesis were incited by observations made by Chesney, Clawson and Webster [2,3,4] in 1928. They observed large hyperplastic goiters in rabbits maintained on cabbage diets. In spite of the fact that these thyroids showed extreme hyperplasia, the animals were found to have low metabolic rates. Though the goiters could be prevented by administering iodine, if iodine was given after the goiter had developed, a severe thyrotoxicosis ensued promptly. Marine, Baumann, Spence and Cipra [5] confirmed this work and also found that the leaves of many brassica plants contained some goitrogenic agent. Since it had been reported that certain nitrile compounds had been isolated from the leaves of several brassicae, Marine [5,6,7,8] and his associates investigated the action of several cyanide compounds on the thyroids of laboratory animals. They observed that methyl cyanide, and several of the other nitriles, produced marked thyroid hyperplasia with low metabolic rates and exophthalmos. Hertz and Roberts [9] have used potassium thiocyanate to produce thyroid hyperplasia. Astwood [10] has also produced thyroid hyperplasia in animals treated with potassium thiocyanate.

Kennedy and Purves [11] have recently reported that rape seed as well as the seed of other brassica plants when fed to rats produce large hyperplastic goiters. Sharpless [12] and his associates have reported that soy bean flour when fed to rats has a strongly goitrogenic action. These soy bean goiters could be prevented by the administration of iodine.

Another group of very interesting and important goitrogens has recently been reported by three different groups of workers. The MacKenzies [13] observed large goiters in animals being treated with sulfaguanidine. At about the same time Richter and Clisby [14] reported their observations of large hyperplastic goiters in animals receiving thiocarbamide. Recently the MacKenzies [15] working in one laboratory and Astwood [1, 10] and his associates in another, have found goitrogenic activity in various other sulfonamides and in molecular compounds similar to thiourea. It was observed, in fact, that most of the sulfonamides are goitrogens as also are many thiourea-like compounds. It is of real importance to note that it was not possible to prevent the action of such goitrogens by means of iodine. Thyroxine, on the other hand, did prevent the goitrogenic action of these drugs. Astwood [10] had previously observed that iodine would prevent the development of goiters in animals treated with potassium thiocyanate.

With the advocated use of soy beans in the modern diet, the liberal prescribing of the sulfonamides in clinical medicine, and with widespread use of thiocyanate in treating hypertension, it becomes of practical importance to know whether such agents have any goitrogenic action in man. It is also of theoretical importance, and of academic interest, to learn as much as possible about thyroid physiology by determining with available tools what we can about the mechanism of such goitrogenesis.

The present report deals with observations made on two patients who developed goiters while receiving potassium thiocyanate for treatment of hypertension. A third case of similar sort was seen in consultation with Drs. R. S. Palmer and D. Kinsey. In this last-mentioned case, that of a woman of 45 years with severe hypertension, a goiter developed after prolonged thiocyanate treatment and disappeared on stopping the drug. It had not redeveloped on resumption of the drug up to September 8, 1943. Barker [16] has also observed goiters develop in a few hypertensive patients being treated with potassium sulfocyanate. His patients had decreased basal metabolic rates and were observed to improve with thyroid therapy even though the drug was continued. The goiters disappeared and the metabolic rates returned to normal. Fahlund [17] has recently reported a case of painful swelling of the thyroid in a patient receiving thiocyanate therapeutically. The swelling and pain disappeared promptly when the drug was stopped. Kobacker [18] has also observed a goiter develop in a patient receiving this drug in treatment of hypertension, as have also Foulger and Rose.[19] Kobacker's case developed myxedema also. The goiter and myxedema disappeared when the drug was stopped but returned when this therapy was resumed. Though the evidence for cabbage and thiocyanate

goiters being on the basis of identical mechanisms is lacking, it is of interest to refer to Suk's [20] report of large goiters occurring endemically in a central European community where cabbage is a principal dietary item.

CASE REPORTS

Case 1. Mr. R. D., a 35-year-old white W.P.A. laborer, entered the medical out-patient clinic of the Massachusetts General Hospital on June 24, 1940, complaining of headaches and of ankle edema. He gave a history of nephritis nine years previously. For three months prior to admission he had been dyspneic and had had pedal edema. He had had severe headaches for three weeks previous to admission. Examination revealed moderate hypertension with some enlargement of the heart to the left. A systolic murmur was heard at the apex. A few râles were heard in both bases. The thyroid was not enlarged. Some nicking of the retinal vessels was observed. During a three month period of symptomatic treatment his blood pressure varied between 190 mm. Hg systolic and 110 mm. diastolic and 220 mm. systolic and 130 mm. diastolic. The headaches persisted.

On September 19, 1940, he was instructed to take potassium sulfocyanate in syrup of wild cherry. The daily dosage of potassium thiocyanate varied between 0.15 gm. and 0.45 gm. The blood cyanate levels during the period of treatment averaged 5.8 mg. per cent. The highest blood level recorded was 8.3 mg. per cent. While taking the thiocyanate, his symptoms improved and the blood pressure fell to 130 mm. Hg systolic and 110 mm. diastolic.

One year after beginning the thiocyanate treatment the patient returned to the clinic complaining of a painless swelling in his neck and of some swelling of his eyes. He entered the hospital on October 7, 1941. On closer questioning the patient admitted that for several months he had had some intolerance to cold and easy fatigue. He also reported a loss of libido. The patient's wife reported that she had observed some dulling of the patient's sensorium. The neck swelling was found to be a very hard diffusely enlarged thyroid which was estimated to be 8 to 10 times the normal size. It was hard enough strongly to suggest malignancy. A loud bruit was heard over it. Moderate exophthalmos with a bilateral lid lag was readily demonstrated. No tremor was present.

The basal metabolic rate was found to be minus 17. Plasma protein iodine was reported as 2.7 gamma per cent. In our laboratory this level of plasma iodine is within the range of levels observed in myxedematous patients.

The ability of the thyroid to collect iodine was determined by means of the radioactive iodine technic of Hertz and Roberts.* Of a dose of 1.0 mg. of radio-iodine given October 15, 20 per cent was excreted in the urine in the first 24 hours, and 6 per cent in the second. The total excretion was, therefore, approximately 30 per cent, which is in the range found by Hertz and Roberts in classic Graves' disease, and is less than that of normal persons.

The urine was studied for substances which might stimulate the thyroid. No such material could be found in an acetone precipitate of the urine. An aliquot of the same 24-hour specimen of urine which had been autoclaved before extraction, however, contained about twice as much thyrotropic substance as is usually demonstrated in the urine of normal persons treated in the same manner.

Under local anesthesia a biopsy of the goiter was done. At this operation the thyroid was found to be extremely vascular. Microscopic examination of the biopsy specimen revealed an extremely hyperplastic thyroid with marked papillary overgrowth. The material bore a striking resemblance to that of goiters which Hertz

* We are indebted to the Physics Dept. Massachusetts Institute of Technology for this determination.
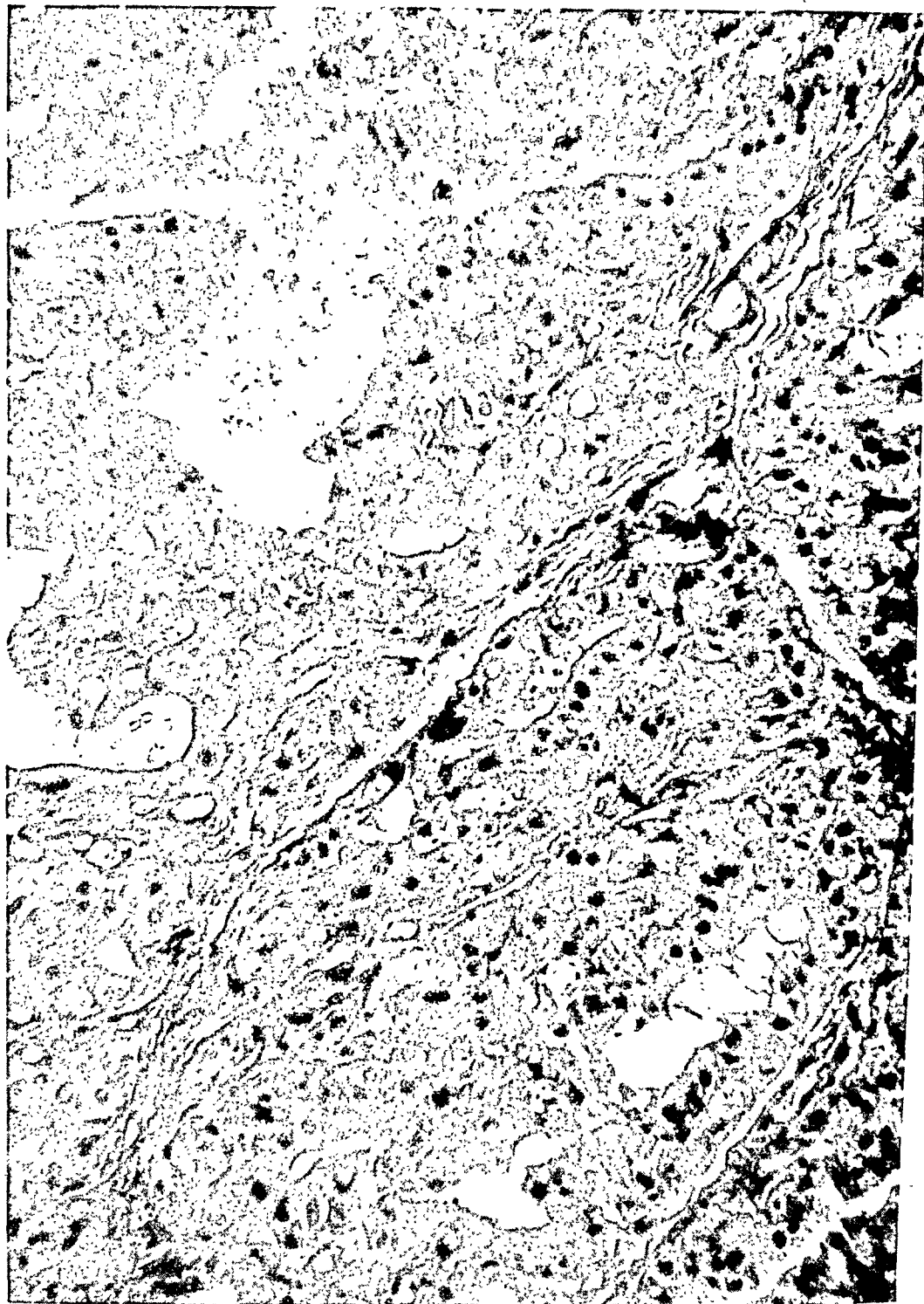
FIG. 1 A. Photomicrograph of thyroid tissue removed at biopsy in Case 1. × 400 diameters.
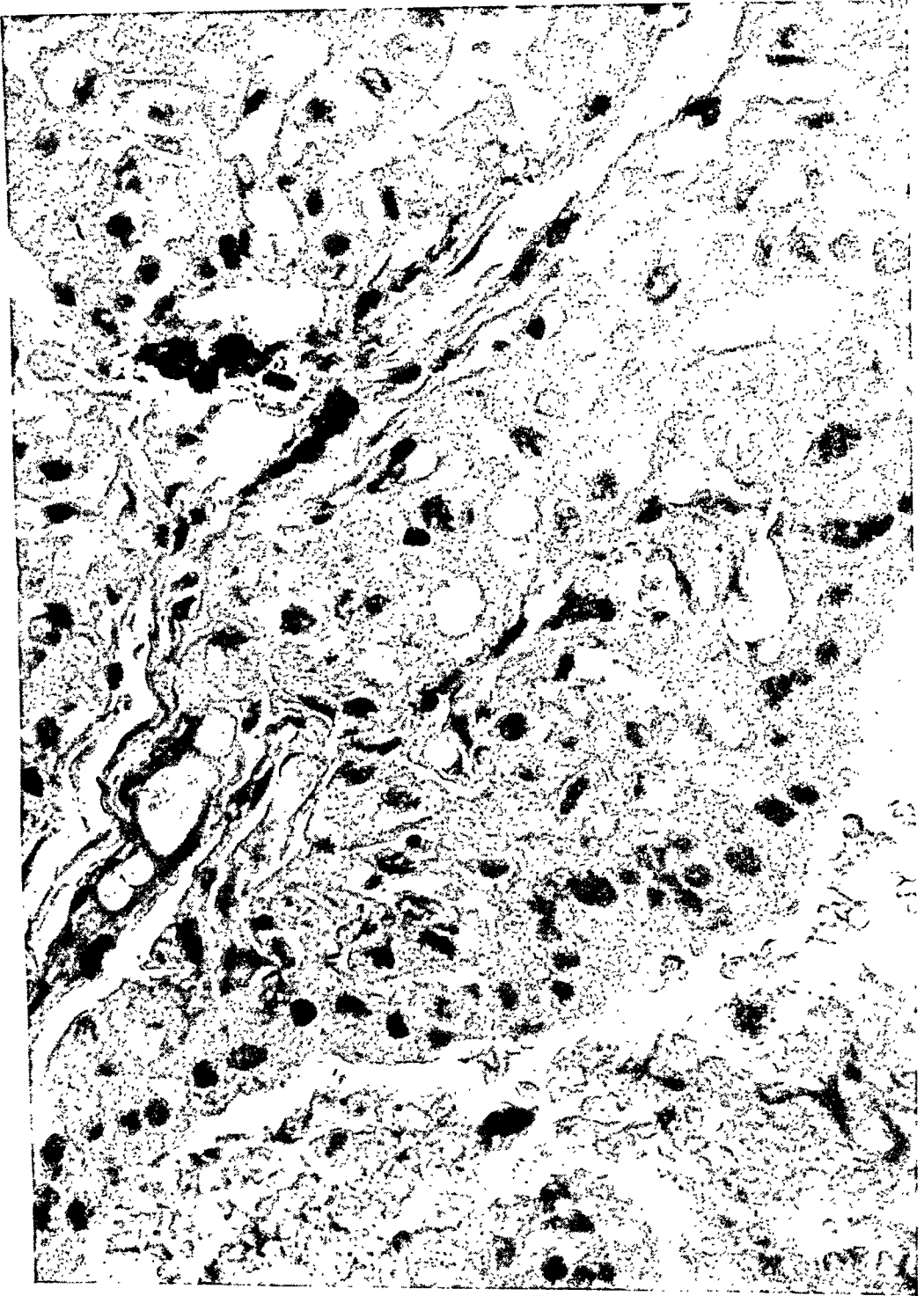
Fig. 1 B. Photomicrograph of thyroid tissue removed at biopsy in Case 1. ×900 diameters.

and Roberts [9] had previously produced in rabbits by the administration of thiocyanate (a report of these studies will be published elsewhere). An explant of the biopsied tissue exposed to thyroid stimulating hormone with tissue culture technics was found to inactivate all of the thyroid stimulating hormone (TSH) in the bathing medium. This inactivation is similar to that observed when thyroid tissue removed from patients with Graves' disease is exposed to TSH in a similar manner, and probably explains our inability to demonstrate any active thyroid stimulating hormone in the unautoclaved urine.

The thiocyanate was stopped. Ten days after stopping the drug the basal metabolic rate had risen to plus 5 and the patient reported that he felt much less fatigued. He also reported that he had a better tolerance for cold. Within three weeks after stopping the drug, the thyroid had regressed in rather remarkable fashion to approximately normal size and the plasma iodine had risen to a normal level. The exophthalmos was less noticeable but the lid lag persisted.

Three months after the medication was stopped the patient returned to the clinic complaining of frequent severe headaches. The blood pressure had risen to 180 mm. Hg systolic and 120 mm. diastolic. Again he was instructed to take potassium thiocyanate in doses of 0.3 gm. daily. He was followed carefully with close observation of his thyroid symptoms, frequent metabolic rates, and with plasma protein iodines. One month after resuming the thiocyanate therapy, the plasma iodine was found to have fallen to a myxedematous level and remained at that level until the drug was stopped. Six weeks after resuming the drug, the patient complained of excessive fatigue, intolerance to cold and of a loss of libido. The lid lag persisted and the exophthalmos became more definite. The thyroid also began to increase in size. These symptoms and findings persisted until the drug was stopped again at the end of nine weeks, at which time the thyroid was estimated to be three times the normal size. No bruit was audible. During this period of observation the basal metabolic rate did not fall below normal. Ten days after the drug was stopped, the plasma iodine had returned to a normal level. The patient reported that he was free of fatigue and that he had a better tolerance for cold. He also reported a return of libido. The lid lag remained.

The patient continued without any thiocyanate therapy for a period of three months. He felt well for most of this time and was free of the headaches which originally had been his primary complaint. His blood pressure began to rise gradually and finally reached a level which previously had produced headaches, i.e., 174 mm. Hg. systolic and 104 mm. diastolic. He then was instructed to take KSCN in syrup of wild cherry. The dose of KSCN was 0.3 gm. daily. He was also instructed to take U.S.P. thyroid 0.1 gm. daily. The blood pressure was lowered again to a level of 142 mm. Hg systolic and 92 mm. diastolic. While taking 0.1 gm. daily of U.S.P. thyroid with the same amount of KSCN as previously he had the desired beneficial effect on his hypertension without developing the signs suggestive of hypothyroidism observed with the previous trial with this drug. Four months after starting the drug, with the onset of cold weather he did complain of some intolerance to cold and of an increased need for sleep as well as of loss of libido. The dose of thyroid prescribed was increased to 0.2 gm. daily. He continued to take the thiocyanate and the thyroid 0.2 gm. daily. On such a régime he has continued to get the desired effect on his hypertension and has remained free of hypothyroid symptoms.

Case 2. Mrs. D., a 34-year-old white American housewife, was admitted to the medical wards of the Massachusetts General Hospital for study of hypertension.

The patient had gone through an uneventful childhood with the exception of migraine headaches which began at the age of 11. She gave no history of scarlet fever, prolonged or recurrent sore throats, or any other debilitating illness. She had first been told that she had hypertension by her family physician at the age of 18, 16 years before entry.

Eight years before admission for study, in 1933, the patient became pregnant for the first time. After the third month of pregnancy she was found to have albumin in the urine, and her blood pressure was said to be rising. Labor was induced in the seventh month. She was delivered of a live child and had a normal recovery. Her blood pressure returned to normal. He second pregnancy followed two years later. This pregnancy likewise was associated with albuminuria and an increase in blood pressure. Again labor was induced in the seventh month and a live child was de-
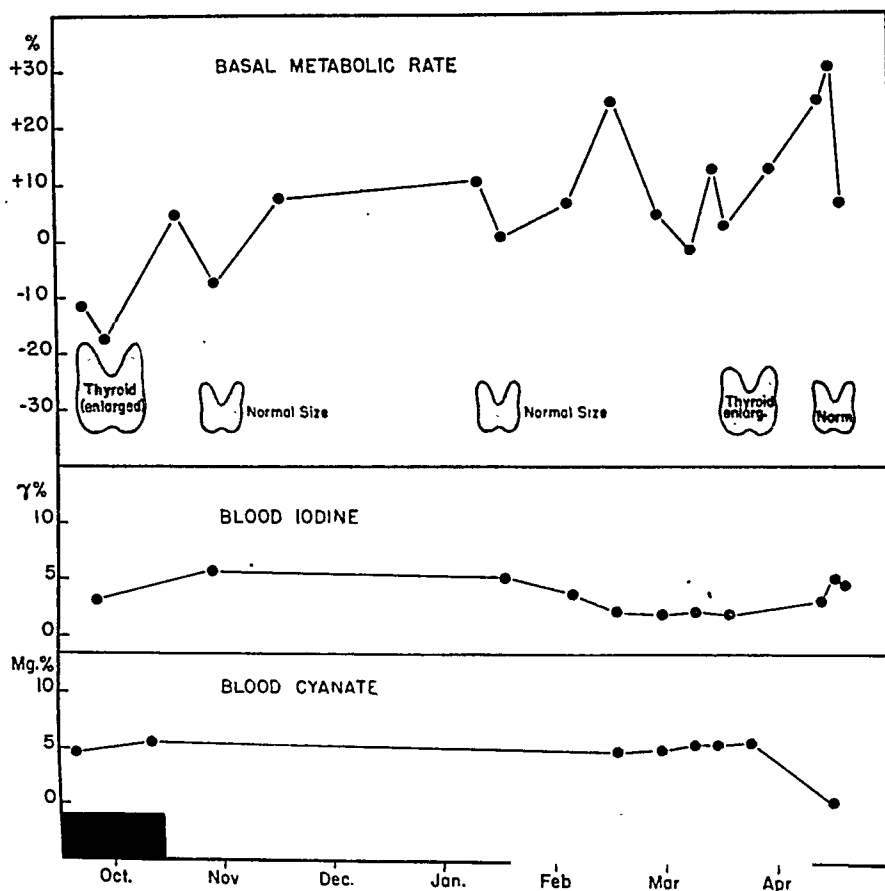
FIG. 2. Basal metabolic rate, blood iodine level, blood cyanatic level and thyroid size in Case 1. The left-hand black rectangle denotes administration of 0.45 gm. of potassium thiocyanate daily; the right-hand rectangle 0.3 gm. daily.

livered. The blood pressure again returned to normal following delivery. The third pregnancy was normal, and was terminated with the normal delivery of a full term baby.

The fourth pregnancy was terminated in the eighth month with a Caesarian section because of signs of severe toxemia associated with hypertension. This delivery was followed by phlebitis. The blood pressure following this pregnancy did not return to normal and the patient continued to show a slight trace of albumin. She was referred to the Massachusetts General Hospital for consideration of surgical treatment of her hypertension.

The inventory by systems revealed a history of pleurisy two years previously and a story of exertional urinary incontinence.

Physical examination showed a rather pale, well developed white woman. The fundi showed slight sclerosis of the retinal vessels. The heart was slightly enlarged

in the region of the left ventricle by physical examination and this was verified by roentgenographic examination. There was a soft systolic murmur heard at the apex. The blood pressure was 150 mm. Hg systolic and 100 mm. diastolic. The left leg was found to be swollen and edematous. The thyroid was described as of normal size.

Her blood pressure was found to be labile by the cold pressor test, the sedative test and with postural changes. She concentrated urine to 1.020. She excreted phenolsulphonphthalein 30 per cent in 15 minutes and 73 per cent in two hours.

Because of subsiding thrombophlebitis it was decided to postpone operative treatment for six months. She was discharged from the hospital to be followed in the hypertension clinic.

Three months later she returned to the medical clinic complaining of rather severe and frequent headaches. Her blood pressure at that time was found to be 180 mm. Hg systolic and 120 mm. diastolic. She was instructed to take potassium sulfocyanate 0.3 gm. daily in syrup of wild cherry. Blood levels of sulfocyanate never were observed to exceed 4.7 mg. per cent. Her blood pressure fell to 130 mm. Hg systolic and 80 mm. diastolic. Four months after starting to take the thiocyanate the patient returned to the medical clinic complaining of feeling tired and slowed down. She was found to have a diffusely enlarged thyroid which was estimated to be about three times the normal size. It was firm and smooth. No bruit was heard. No eye signs were observed. The thiocyanate was stopped and the patient was re-admitted to the hospital for study two weeks later.

When the patient was admitted to the hospital, she was found to have a goiter as described in the Out Patient Department. She reported that this had been present for about six weeks. She denied any intolerance for the cold but did report that she had gained 22 pounds of weight since her discharge from the hospital eight months previously. Her metabolic rate upon admission to the hospital was found to be minus 12. She was again given KSCN 0.3 gm. daily. Her metabolic rate fell within 12 days to minus 32. The goiter, however, did not get larger. Indeed, it was the opinion of the service that it had grown somewhat smaller. Her blood pressure while in the house varied between 132 mm. Hg systolic and 90 mm. diastolic, and 120 mm. systolic and 88 mm. diastolic. The blood cholesterol was not elevated. It was reported as 179 mg. per cent. The plasma iodine was determined by Dr. W. T. Salter at Yale School of Medicine and was reported by him to be 2.8 gamma per cent. This level is within the range observed in patients with myxedema.

In this case also a search was made for thyroid stimulating properties in the urine. None, however, could be demonstrated in an acetone precipitate. However, as in Case 1, when an equal aliquot of the same urine was autoclaved, about twice as much thyrotropic activity developed as is usually found in the autoclaved urine of normal people. Unfortunately the patient would not consent to a biopsy of the thyroid.

The patient was discharged with instructions to continue taking the thiocyanate and to be followed in the thyroid clinic.

In the out-patient department the basal metabolic rate was found to have risen to minus 15 where it remained. The patient presented the picture of a myxedematous individual. The thyroid remained about twice the normal size. No eye signs were observed. Two months after her discharge from the hospital, she was instructed to continue with the thiocyanate therapy and to take U.S.P. thyroid 0.1 and 0.2 gm. on alternate days. After thyroid was added to her régime, the metabolic rate rose to minus 6 and her thyroid returned to normal size within two months. The picture of myxedema disappeared. The blood pressure remained at a satisfactory low level of 114 mm. Hg systolic and 74 mm. diastolic.

DISCUSSION

We are aware that any assumption that experimental cabbage goiters, brassica seed goiters and cyanide goiters are on the basis of the same mechanism as are the goiters that we have observed in thiocyanate treated patients, is an apriority. However, if we compare the observations made on these two patients with those made on animals treated with agents which are thought to be similar, we may formulate certain hypotheses as to the mechanism of such goitrogenesis.

Our observations may be epitomized as follows. We have observed goiters develop in two patients who were receiving potassium thiocyanate for treatment of hypertension. These goiters were associated with decreased thyroid function as evidenced by clinical symptoms of hypothyroidism, low basal metabolic rates, and plasma protein iodine levels of the sort usually observed in patients having myxedema. Histological examination of biopsy material removed from one of these patients revealed an extreme hyperplasia of the thyroid. One patient developed exophthalmos with lid lag. In one patient the goiter, as well as the clinical and laboratory evidences of hypothyroidism, disappeared when the thiocyanate administration was stopped, but returned when the drug was taken again. In both cases the goiters and clinical signs of hypothyroidism disappeared when thyroid was administered though the administration of thiocyanate was continued.

Webster and Chesney [4] and Marine [5] and associates found that they could prevent the development of goiters in animals receiving a cabbage diet or methyl cyanide if thyroid or iodine were administered at the same time. The former investigators also reported that if iodine were administered to animals with large cabbage goiters, the picture changed from that of myxedema to that of severe thyrotoxicosis, which in some instances was fatal. The observed decreased amount of labeled iodine excreted in the urine of our first patient probably indicates an increased avidity of this type of goiterous tissue for iodine. A hunger for iodine of this degree is seen as a rule only in untreated classic thyrotoxic patients. The above phenomenon described by the Baltimore investigators is probably on the same basis as is this observed increased uptake of iodine by the cyanate goiterous tissue. Griesbach, Kennedy and Purves [21, 22] reported that the pituitaries of animals having goiters produced by a brassica seed diet presented histological changes similar to those observed in the pituitaries of thyroidectomized animals. They also reported that goiters could not be produced in hypophysectomized animals fed the same diet.

It would seem then, that the thyroid hyperplasia is secondary to an increased secretion of the thyroid stimulating hormone of the pituitary (TSH). No free active TSH was demonstrable in the urine of our patients. We feel that this is due to an inactivation of the pituitary hormone by the hyperplastic thyroid tissue. This is evidenced by our observation that explants of the biopsy tissue taken from our first patient's goiter inactivated as much

TSH exposed to the tissue in bathing medium as does the thyroid tissue of Graves' disease.[23]   The thyrotropic effect of urine which had been autoclaved before extraction was very definite and amounted to about two times that observed in the autoclaved urine of normal human beings.   We interpret this observation as a reactivation of TSH which had been inactivated by the thyroid cells.   (The reactivation of TSH will be discussed in a subsequent communication.)   These observations would indicate that there is an increased activity of the pituitary in states of thiocyanate goiter.   Such increased pituitary activity is probably due to an induced hypothyroidism.

There are various theories to explain the action of these agents in producing the hypothyroid state.   Marine [24] and associates suggested that the agents used by them interfered with the action of the thyroid hormone by disrupting the cellular oxidation systems of tissue cells, in other words, an end organ effect, and thereby produced a lowered metabolism of the entire organism. Williams and Bissell [25] also adhere to this interpretation.   It was postulated that such a lowered metabolism would stimulate the pituitary via the hypothalamus, to secrete an increased amount of TSH.   This explanation seems untenable because of our own observations, and because of those reported by Barker [16] that the goiters and symptoms of lowered metabolism disappeared when thyroid was administered, although the thiocyanate therapy was continued.   Dr. J. Lerman [26] has made an isolated observation that also is in disagreement with Marine's theory.   He administered potassium thiocyanate to a controlled myxedematous patient who was receiving a standard dose of U. S. P. thyroid.   The thiocyanate did not cause any fall in the basal metabolic rate.

The low levels of plasma iodine observed in our patients indicate decreased circulating thyroid hormone and should direct our attention to some interference with the formation of normal thyroid hormone as a possible explanation for the induced hypothyroidism.   These low levels of plasma iodine constitute further evidence against the theory that end-organ sensitivity is reduced by cyanate.   Were end-organ sensitivity reduced, the plasma iodine reflecting as it does, thyroid hormone level, should be increased.   The experimental observations that goiters cannot be produced in laboratory animals with potassium thiocyanate nor with the other similar goitrogens if iodine is administered suggest that the decrease in circulating thyroid hormone is due to some interference with normal iodine metabolism.   This interference with iodine metabolism might be due simply to a diversion from the thyroid of exogenous iodine by this group of goitrogens.   Supposing such an action actually to be the mechanism, then it can be further supposed that iodine, when administered in excess, will displace the goitrogen in a similar fashion.

Another possible explanation is that of a paralysis, or inactivation, of the enzyme systems, the functions of which are those of iodinating the thyroid hormone.   Thus it would appear that a hypothyroid state would result from the secretion of a non-iodinated thyroid hormonal skeleton, i.e., thyronine or

a thyronine-like substance.   The thyronine-like substance being non-iodinated would have no calorigenic action and would therefore permit the rate of metabolism to fall to the level of a thyroidectomized organism.   The low metabolic rate would in turn cause stimulation of the pituitary to increase its secretion of thyroid stimulating hormone.   The absence of the thyroid
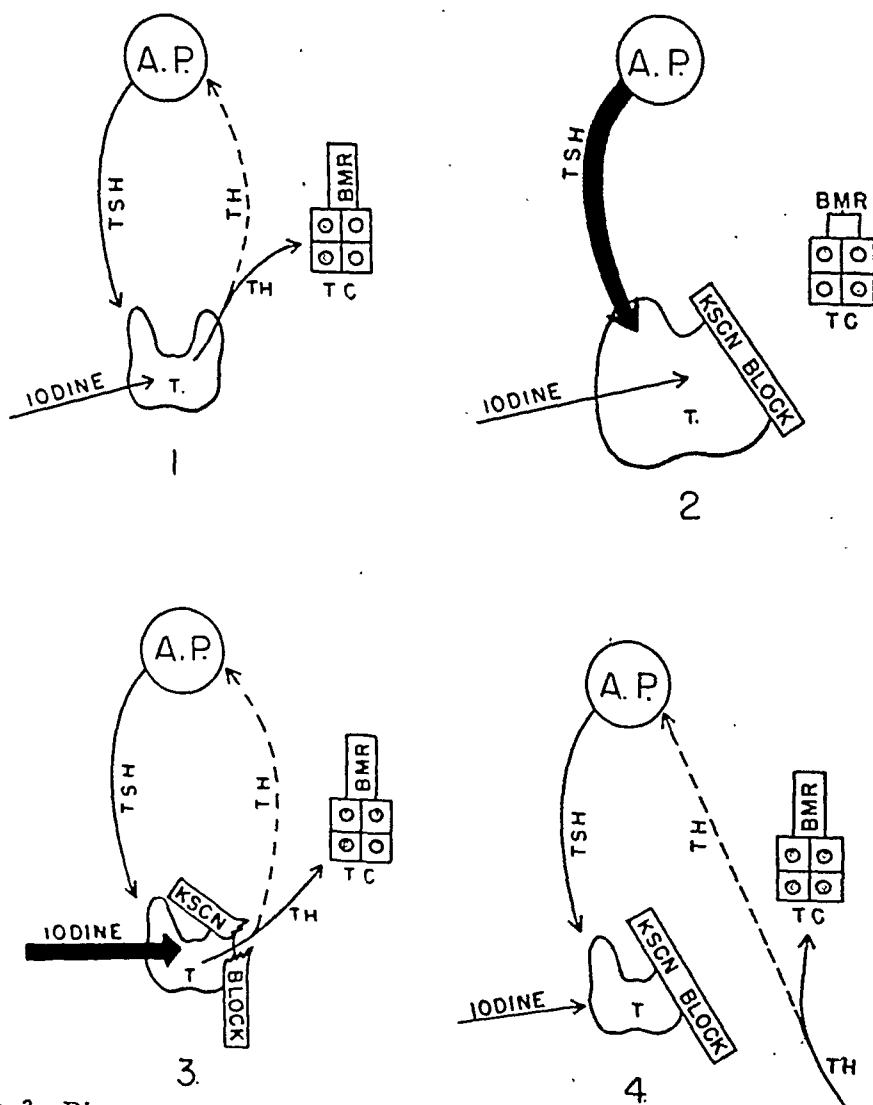
FIG. 3. Diagrammatic representation of the effect of cyanate on the pituitary-thyroid axis.

1. Normal relationships. The anterior pituitary—AP—by means of its hormone—TSH —and in the presence of an adequate supply of iodine, stimulates the thyroid—T—to produce its hormone—TH—which stimulates the metabolism of tissue cells—TC—and inhibits AP.
2. Cyanate imposes an obstruction to the completion of TH. The BMR of TC therefore falls, and the uninhibited AP produces an excess of TSH. This causes hyperplasia of T, but since the block remains, no active TH is delivered to the body.
3. The supply of an excess of iodine forces the cyanate block so that TH is made in adequate amounts, BMR remains normal and TSH formation remains normal, and therefore no enlargement of T takes place.
4. The supply of TH from without by-passes the cyanate block so that BMR remains normal and TSH formation remains normal, as does the thyroid gland.

hormone would permit the pituitary to elaborate the TSH without any inhibition. In response to the abnormal stimulation with TSH the thyroid would respond with a marked hyperplasia and would secrete increased amounts of non-iodinated thyroid protein (figure 3). The theory of the non-iodinated thyroid hormone could account for the experimental observation that laboratory animals having large cabbage goiters promptly develop severe thyrotoxicosis when iodine is administered. This theory seems tenable in the light of our present information and is compatible with the observations made in patients who developed goiters while taking thiocyanate therapeutically as well as with those observations on animals made goiterous by the administration of this group of agents. It is very likely that a greater knowledge of thyroid cellular physiology will permit the formulation of more elaborate, and no doubt more intelligent, theories as to the mechanism of the goitrogenesis of such agents.

The exophthalmos produced in rabbits treated with methyl cyanide by Marine [8, 24] and his associates gave rise to considerable speculation concerning the mechanism of exophthalmos. Because of observations made on similar exophthalmic animals after treatment with pituitary extracted thyrotropic hormone, they postulated that the exophthalmos as well as the thyroid hyperplasia was due to increased pituitary activity in secreting TSH. In view of the observations of Griesbach, Kennedy and Purves [21, 22] referred to above, it seems tenable that the exophthalmos is on the basis of increased pituitary activity. It is interesting that only one of our patients developed exophthalmos. Again we have the suggestion that the response of an organism to hormonal treatment or secretion is dependent on the state of the end-organ.

On the practical side one is entitled to ask why is thiocyanate goiter not more common in persons being treated with thiocyanate for hypertension? The answer that suggests itself, but that cannot be proved is that iodine occurring naturally in most environments is usually sufficient to prevent it. One is led to guess further that had thiocyanate been used widely in endemic goiter regions prior to the introduction of iodized salt there might have been considerable thiocyanate goiter.

In the field of therapeutics it can be pointed out that in the treatment of hypertension with thiocyanate over long periods of time the administration of prophylactic doses of iodine should prevent the development of thiocyanate goiter. Also when thiocyanate goiter has developed, it is not necessary to discontinue the administration of thiocyanate, which may be essential from the point of view of the blood pressure, it is merely necessary to give thyroid along with it. One can thus get the desirable effect of thiocyanate on the blood pressure and stop the undesirable effect upon the thyroid gland.

SUMMARY

1. Two cases of thiocyanate goiter in man are reported. Note is made of a third seen in consultation. Several from the literature are cited.

2. Thiocyanate goiter is characterized by (a) hyperplasia of the thyroid; (b) symptoms of hypothyroidism; (c) exophthalmos (seen in one case); (d) low basal metabolic rate; (e) low blood iodine; (f) decreased urinary excretion of labeled iodine; (g) increased urinary excretion of thyrotropic hormone in the inactivated form.

3. The theory is advanced that this drug blocks the formation of thyroid hormone by the thyroid, and that the consequent lowering of concentration of active thyroid hormone in the blood stream causes stimulation of the anterior pituitary to produce an excess of thyrotropic hormone. This in turn causes thyroid hyperplasia but, because of the block, no increase in physiologically active thyroid hormone output. It is a hyperplasia of frustration. An excess of administered iodine may force the block, and cause liberation of active hormone. Administration of thyroid by-passes the block, and relieves the situation by substitution.

4. Thiocyanate goiter can probably be prevented by prophylactic doses of iodine.

5. Thiocyanate goiter can be relieved by the administration of thyroid even when thiocyanate administration for hypertension is continued.

BIBLIOGRAPHY

1. ASTWOOD, E. B., SULLIVAN, J., BISSELL, A., and TYSLOWITZ, R.: Action of certain sulfonamides and of thiourea upon the function of the thyroid gland of the rat, Endocrinology, 1943, xxxii, 210.

2. CHESNEY, A. M., CLAWSON, T. A., and WEBSTER, B.: Endemic goitre in rabbits. I. Incidence and characteristics, Bull. Johns Hopkins Hosp., 1928, xliii, 261.

3. WEBSTER, B., CLAWSON, T. A., and CHESNEY, A. M.: Endemic goitre in rabbits. II. Heat production in goitrous and non-goitrous animals, Bull. Johns Hopkins Hosp., 1928, xliii, 278.

4. WEBSTER, R., and CHESNEY, A. M.: Endemic goitre in rabbits. III. Effect of administration of iodine, Bull. Johns Hopkins Hosp., 1928, xliii, 291.

5. MARINE, D., BAUMANN, E. J., SPENCE, A. W., and CIPRA, A.: Further studies on etiology of goitre with particular reference to the action of cyanides, Proc. Soc. Exper. Biol. and Med., 1932, xxix, 772.

6. SPENCE, A. W., and MARINE, D.: Production of thyroid hyperplasia in rats and mice by administration of methyl cyanide, Proc. Soc. Exper. Biol. and Med., 1932, xxix, 967.

7. MARINE, D., SPENCE, A. W., and CIPRA, A.: Production of goitre and exophthalmos in rabbits by administration of cyanide, Proc. Soc. Exper. Biol. and Med., 1932, xxix, 822.

8. MARINE, D., and ROSEN, S. H.: The exophthalmos of Graves' disease. Its experimental production and significance, Am. Jr. Med. Sci., 1934, clxxxviii, 565.

9. HERTZ, S., and ROBERTS, A.: Personal communication.

10. ASTWOOD, E. B.: The chemical nature of compounds which inhibit the function of the thyroid gland, Jr. Pharmacol. and Exper. Therap., 1943, lxxviii, 79.

11. KENNEDY, T. H., and PURVES, H. D.: Studies on experimental goitre. I. The effect of brassica seed diets on rats, Brit. Jr. Exper. Path., 1941, xxii, 241.

12. SHARPLESS, G. R., PEARSONS, J., and PRATO, G. S.: Production of goitre in rats with raw and with treated soy bean flour, Jr. Nutrition, 1939, xvii, 545.

13. MACKENZIE, J. B., MACKENZIE, C. G., and McCOLLUM, E. V.: The effect of sulfanilyl-guanidine on the thyroid of the rat, Science, 1941, xciv, 518.

14. RICHTER, C. P., and CLISBY, K. H.: Toxic effects of the bitter tasting phenylthiocarbamide, Arch. Path., 1942, xxxiii, 46.
15. MacKENZIE, C. G., and MacKENZIE, J. B.: Effect of sulfonamides and thioureas on the thyroid gland and basal metabolism, Endocrinology, 1943, xxxii, 185.
16. BARKER, M. H., LINDBERG, H. A., and WALD, M. H.: Further experiences with thiocyanates. Clinical and experimental observations, Jr. Am. Med. Assoc., 1941, cxvii, 1591.
17. FAHLUND, G. T. R.: Painful enlargement of the thyroid gland as a manifestation of sensitivity to thiocyanate, Proc. Staff Meet. Mayo Clin., 1942, xvii, 289.
18. KOBACKER, J. L.: Production of goitre and myxedema by sulfocyanates, Ohio State Med. Jr., 1942, xxxviii, 541.
19. FOULGER, M. P. H., and ROSE, E.: Acute goiter during thiocyanate therapy for hypertension, Jr. Am. Med. Assoc., 1943, cxxii, 1072.
20. SUK, V.: Cabbage and goitre in Carpathian Ruthenia, Anthropologie, Praha, 1931, ix, 1.
21. GRIESBACH, W. E.: Studies on experimental goitre. II. Changes in the anterior pituitary of the rat, produced by brassica seed diet, Brit. Jr. Exper. Path., 1941, xxii, 245.
22. GRIESBACH, W. E., KENNEDY, T. H., and PURVES, H. D.: Studies on experimental goitre. III. The effect of goitrogenic diet on hypophysectomized rats, Brit. Jr. Exper. Path., 1941, xxii, 249.
23. RAWSON, R. W., GRAHAM, R. M., and RIDDELL, C. B.: Physiological reactions of the thyroid-stimulating hormone of the pituitary. II. The effect of normal and pathological human thyroid tissues on the activity of the thyroid stimulating hormone, ANN. INT. MED., 1943, xix, 405–414.
24. MARINE, D., ROSEN, S. H., and CIPRA, A.: Further studies on the exophthalmos in rabbits produced by methyl cyanide, Proc. Soc. Exper. Biol. and Med., 1933, xxx, 649.
25. WILLIAMS, R. H., and BISSELL, G. W.: Thiouracil in the treatment of thyrotoxicosis, New England Jr. Med., 1943, ccxxix, 97.
26. LERMAN, J.: Personal communication.

ACUTE LUPUS ERYTHEMATOSUS DISSEMINATUS *

By Harley E. Cluxton, Jr.,† M.D., and Louis A. M. Krause, M.D.,
F.A.C.P., *Baltimore, Maryland*

In comparatively recent years much attention has been given to the symptom-complex called acute lupus erythematosus disseminatus. The purpose of this paper is to present a concise review of the literature on this subject with emphasis on its clinical aspects.

Synonyms: Visceral erythema group (Osler [1]), disseminated lupus erythematosus, atypical verrucous endocarditis (Libman-Sacks [2]), fever of unknown origin (Christian [3]), and diffuse peripheral vascular disease (Baehr and others [4]).

Definition: Lupus erythematosus disseminatus acutus is a clinical entity even though the name emphasizes only one of several characteristic symptoms of the syndrome. It is a disease of unknown etiology associated with widespread visceral lesions predominantly involving the kidneys, lymph nodes, blood vessels, serous and endocardial surfaces, as well as the skin.

History: Kaposi [5] in 1872 first pointed out the acute disseminated form of lupus erythematosus. He also called attention to the fact that the chronic form can become acute. In 1895 Sir William Osler [6] reported under the name erythema exudativum multiforme a group of cases with polymorphic erythematous skin lesions associated with a variety of visceral lesions such as acute nephritis, gastrointestinal or urinary bleeding and splenomegaly, endocarditis and pericarditis. Osler's case number 19, with lesions of lupus erythematosus and erysipelas-like eruption (Kaposi's erysipelas perstans faciei) and number 26, with lupus erythematosus lesions, both of whom died with evidences of nephritis, were probably identical with, or variants of, acute disseminated lupus erythematosus. Fordyce [7] in 1899 first described the capillary thrombosis and the aggravating effect of frost bite and sunburn on the lesions. In 1911 Libman first recognized the existence of a peculiar clinicopathologic entity, which he and Sacks reported in 1924 [2] as a "hitherto undescribed form of valvular and mitral endocarditis" or "atypical verrucous endocarditis." They went on to say that "it is not improbable that a certain relationship exists between the atypical form of endocarditis and certain of these cases included in the erythema group." Keefer and Felty [8] reported three fatal cases of acute disseminated lupus erythematosus with autopsy of two in 1924. Since these early reports an ever increasing number of cases have been, and are being, reported in the literature because a clinical entity has been established.

Incidence: The disease is not common, but most of the larger hospitals have had several cases at one time or another. It occurs most frequently among peoples living in the northern climates (Kierland[9]).

Race: The white race seems more susceptible to the disease. However, two of the three cases reported by Keefer and Felty[8] were negroes.

Sex: There is a marked predilection for females. Kierland[9] finds that 77 per cent of the acute lupus erythematosus disseminatus cases are in women. A few cases have been reported in males. Rose and Pillsbury[10] in their study of 12 cases found three cases that were males. Baehr[4] et al. reported only one male in their series of 23 cases.

Ginzler and Fox[11] reported a case of acute lupus in a 17 year old male of Anglo-Scotch birth. One of Madden's[12] five cases was a male.

Age: Steward and Goeckerman,[13] after a careful search in the literature up to 1931, found only four cases under 15 years of age. Madden[12] in 1932 reported a case in a boy five years of age; "the patient was exhibited at an annual meeting of the Minnesota Dermatological Society, and the diagnosis was concurred in by all the members present." The average age group is in the second or third decade, most frequently about 25 years of age.

Duration: The duration is quite variable because death is usually due to complications. It ranges from a few weeks to several years, the average duration being 18 months. Reifenstein et al.[14] in their report of 17 cases found no demonstrable correlation of duration with severity and extent of pathologic lesions. Some of the most severe lesions occurred in cases in which the clinical course could not be traced back farther than a few months.

The mortality of the disease is high; more than 90 per cent of cases end fatally within five years. A striking characteristic is the tendency for acute cutaneous and systemic manifestations to appear or recur after exposure to sun or ultraviolet light, roentgen-rays, cold, or the intracutaneous injection of irritating substances such as tuberculin.

General Characteristics: Acute lupus erythematosus disseminatus is characterized by all or many of the following features: erythematous cutaneous lesions, polyarthritis, prolonged fever, leukopenia with secondary anemia, polyserositis, endocarditis, nephritis and a remittent cachectic course, with a fatal termination weeks to several years after the onset.

The clinical course is extremely variable, since termination is usually the result of some complication. A patient who is apparently moribund may occasionally improve to such a degree that he or she may be discharged from the hospital as cured, only to return weeks or months later and go rapidly to exitus. On the other hand, a patient may have a small erythematous lesion which will initiate a fulminating and rapidly fatal illness. The clinical picture may be preceded by arthralgia, malaise, recurrent bouts of fever or other vague symptoms of ill-health over a prolonged period. Sometimes there is a history of seasonal bouts of skin lesions occurring in the summer after undue exposure to the sun.

Skin Lesions: The butterfly distribution of the skin lesions is a description that was, at one time, overemphasized. The distribution and sequence of involvement of the skin areas vary somewhat; however, the usual sequence is face, neck, hands, extremities and trunk. The moist surfaces, including the labia majora may become involved and present distressing symptoms (Madden's case 2 [12]). At times the skin lesions may closely imitate those occurring in acute pellagra, erysipelas and erythema multiforme (Weidman and Gilman [15]).

The eruption begins as erythematous patches which tend to coalesce and cover a large area. The lesions are clearly demarcated, dusky red, and have a bluish tinge. The erythema is essentially fixed whereas that seen in erysipelas is migratory. Baehr [4] noted also that the erythema is characteristically located on the ends of the fingers, around the nail beds, on the thenar and hypothenar eminences, and occasionally on the ends of the toes and the ball of the foot. The follicular orifices are dilated and often plugged. As atrophy ensues there appears a fine, gray, firmly adherent scale. Depending upon the amount of edema, the lesions may become papular, vesicular or bullous. When the superficial vessels become thrombotic or their walls injured by trauma, hemorrhagic lesions in the form of purpura-like macules, vesicles and bullae occur. At the height of the disease, the patients often show erythematous or petechial areas on the mucous membranes, particularly the mouth. These soon develop into small ulcers surrounded by an erythematous or hemorrhagic areola. They are prone to ulcerate and discharge purulent material. Marked pigmentation of the face is common during remission, and diffuse alopecia is the rule (Belote [16]).

Most dermatologists divide the lesions of lupus erythematosus roughly into two groups, the chronic discoid form and the acute disseminated variety.

The chronic or discoid form of lupus erythematosus is generally recognized as of slow growth and commonly associated with a good prognosis as far as life is concerned. However, it occasionally disseminates as result of overexposure to sunlight or gold therapy; and when it does, it takes on the same characteristics as the acute form. Stokes [17] warns that when the eruption of chronic lupus erythematosus begins to spread from the face to other parts, or to be associated with marked involvement of the mucous membranes, disseminated lupus erythematosus impends. He describes such an occurrence in a 39 year old white man who had had the chronic form for two years. Belote [16] considers the acute and chronic types as manifestations of the same disease.

O'Leary [18] subdivides the acute disseminated variety into: (a) generalized discoid or chronic disseminate, (b) subacute disseminate, (c) acute disseminate. Distinction between the subacute and acute is relative and depends on the severity and duration of the skin lesions and systemic symptoms.

The skin lesions in all types of lupus erythematosus are described as being painless. Mild itching or burning are usually the only cutaneous subjective symptoms which may occur during periods of increased activity (Kierland [9]).

The question often arises as to whether the visceral lesions of the acute disseminated lupus erythematosus syndrome may exist in the complete absence of cutaneous lesions. Baehr,[4] Libman and Sacks,[2] Friedberg,[19] and Tremaine[20] report cases in which the skin lesions appeared some months after the clinical symptoms.

Arthritis: Arthralgia is usually present at one time or another. It may precede or accompany the skin lesions and systemic phases of the disease. Slocumb[21] found the incidence of joint involvement in the chronic disseminated, subacute disseminated and acute disseminated forms to be 20 per cent, 57 per cent and 63 per cent respectively. In eight of his patients, the joint symptoms preceded the skin lesions by one and one-half months to five years. One of the Cabot cases in the New England Journal of Medicine[22] had mild attacks of pain in the shoulders and hands which occurred every spring and lasted about two weeks for a period of 11 years. Mallory[23] found that the joints showed marked synovitis but no evidence of rheumatoid arthritis.

The characteristic features are pain, swelling and tenderness of the joints with slight elevation of the surface temperature without redness. Joint deformities usually late and involving the smaller joints of the extremities have been reported by Tremaine[20] and Friedberg et al.[19]

However, Mallory[23] says "it is quite unusual in lupus to see permanent changes in the involved joints." The signs and symptoms do not seem to respond to the usual therapeutic measures.

The pathological studies of the joints reported have been meager. Tremaine[20] reported a case in which there was hypertrophy of the synovial villi, subperiosteal bone formation and inflammation with perivascular infiltration of inflammatory cells of the subsynovial and capsular tissues. Two cases reported by Friedberg et al.[19] had similar articular and extra-articular swelling associated with endothelial hyperplasia and cellular inflammation which contained giant cells and a few gram-positive cocci. The larger joints are usually affected. Ginzler and Fox[11] found only slight hyperplasia of the synovial lining cells in sections from the synovial tissues and articular cartilages of the right knee.

Fever: The fever is prolonged and remittent. During the acute phase of the disease it is usually sustained and often high. The pulse rate is proportionate to the temperature and has no particular significance.

Associated with the fever is malaise, profound prostration, sweats usually out of proportion to the demonstrable findings, and weight loss. According to Keil[24] systemic lupus erythematosus is usually free from involvement of subcutaneous tissue in any definite manner and the rapid weight loss encountered is probably the result of numerous factors.

Blood: The blood usually shows evidence of a depression of the bone marrow function, leukopenia, thrombopenia and a moderate anemia. The cause of the depression in the bone marrow is not definitely known. It may

be due to a toxic damage or to vascular lesions in the marrow. Leukopenia is often cited as a principal feature of the blood picture; however, Bauer [25] states that only 30 per cent of the 65 cases at the Massachusetts General Hospital had low leukocyte counts. Except in the event of superimposed infection or complication, one does not find a leukocytosis. Rose and Pillsbury [10] claim there is a roughly uniform reduction in the number of all the leukocyte forms, with perhaps some tendency toward a relative increase in neutrophiles.

The sedimentation rate is most often increased and remains so during clinical remissions.

Various chemical analyses of the blood show no significant changes except for an increased urea nitrogen in cases in which there is azotemia.

It is not uncommon to get false positive tests for syphilis. Davis and Ayman [26] believe the positive Wassermann test is due to a disturbed colloid and lipoid balance of the blood serum. Coburn and Pauli [27] observed in two classical cases that the factor responsible for the anticomplementary reaction was in the globulin fraction which was increased in the serum.

Serous Membranes: Inflammation of the serous membrane of the pleural, pericardial, and peritoneal cavities is of common occurrence. The involvement usually manifests itself by pain, friction rubs, and signs of effusion. All 17 patients reported by Reifenstein et al.[14] showed some evidence of pleuritis. Most of the friction rubs are recorded as pericardial. It is common for signs of pulmonary involvement to be present for many months. According to Klemperer et al.[28] the involvement of the serous membranes is from the beginning a relatively deep process by virtue of primary injury to the connective tissue.

Cardiovascular System: The pathological changes in the heart are not constant. Keil [24] finds there is gross evidence of pathologic changes in the endocardium, both valvular and mural, in approximately 30 to 50 per cent of cases. As a rule, patients with acute lupus erythematosus disseminatus die from complications other than myocardial failure. Clinically the myocardium is usually spared. The most common alteration of the electrocardiogram is low voltage in all leads which is interpreted as damage to the cardiac musculature. Contratto and Levine [29] report a case which had a distinct delay in the A–V conduction throughout the course of the disease. No digitalis was given. They go on to say that this finding in the early course of the disease, before the rash appeared, led them to consider rheumatic fever as the first probable diagnosis.

Gross,[30] in a pathological study of the hearts in a series of 23 cases, found hematoxylin-stained granular bodies especially frequently in the valves and valve pockets. He thinks "the milder, spongy, superficial valvular lesions containing degenerating, ghost-like mononuclear cells are probably earlier stages of the hematoxylin-stained bodies and almost characteristic." According to him these hematoxylin-stained granular bodies have been encountered only in systemic lupus. Klemperer et al.[28] say that these changes described by

Gross are but a part of a complex injury whose essential feature is the degeneration of the noncellular components of the collagenous tissues.

Occasionally the atypical verrucous endocarditis of Libman and Sacks [2] is found. Since their report of four cases in 1924, Gross [31] in 1932 found among 6,000 autopsies, 37 possible cases of Libman-Sacks endocarditis, of 11 of which he was certain; Baehr et al.[4] found 13 cases in their reported series of 23 cases; and in 1940 Gross [30] observed eight cases in a series of 23 cases of acute lupus erythematosus disseminatus. According to Gross [30] the primary and fundamental change in atypical verrucous endocarditis (Libman-Sacks) appears to be in the endothelium. The findings of Klemperer et al.[28] are opposed to this statement of Gross. They say that widespread damage is evident in all layers of the heart by virtue of a basic injury primarily localized in the connective tissues. Aschoff bodies and Bracht-Wachter lesions are absent from the myocardium in the atypical verrucous endocarditis.

Klemperer et al.[28] say it is the connective tissue, primarily, which is injured in acute lupus erythematosus disseminatus. The fibrinoid degeneration of collagen fibers in the adventitia produces the vascular lesions which are a mere local expression of the fundamental connective tissue injury. In contrast to other systemic vascular diseases, such as periarteritis nodosa and malignant sclerosis, the blood pressure usually remains normal. The minute vessels (capillaries) are more commonly involved in acute lupus erythematosus disseminatus.

Renal: Renal involvement is common. Mallory [22, 23] says that nephritis, even though the changes may be minimal, can be found in 70 per cent of the cases. He speaks of the nephritis as being the focal glomerular type in which one may find occasional glomerular tufts or even the single loops of the tufts like those of glomerulonephritis but with many entirely normal glomeruli. Stickney and Keith [32] describe the lesions in more detail. In their series of 15 cases, they found a proliferation of the endothelial cells of the glomerular capillaries with hyaline thickening of these capillary walls and an irregularity and thickening of the basement membrane. They regard these changes as somewhat similar to those found in acute glomerulonephritis and the toxemias of pregnancy. The lesions are considered secondary to the toxic processes and do not represent primary renal disease. Keith [33] summarizes the renal changes as follows: "(1) Renal insufficiency does not play an important rôle causing death, since severe chronic uremia very seldom occurs. (2) The histologic changes in the kidney are almost never as extensive as those seen in cases of progressive glomerulonephritis of similar duration. . . . (3) The usual renal lesions, particularly those of the glomerulus, may resemble the lesions found during the first two weeks of acute glomerulonephritis. But in lupus erythematosus renal anomalies such as albuminuria, cylindruria, and microscopic hematuria may persist for two or three years in contrast to a few weeks in the former condition and yet similar histologic findings be present. This fact suggests that the renal lesion in

lupus erythematosus is a mild reaction to a toxic agent with minimal scar formation. (4) Further study has indicated that this renal lesion is non-specific and can be produced in various toxic conditions as, for example, lupus erythematosus, ulcerative colitis and peritonitis. (5) Finally, we have observed in some of these cases albuminuria varying periodically from grades 1 to 4 and at necropsy only minor histologic changes in the glomerulus. Such findings suggest that the renal lesion may be temporarily reversible and analogous to what sometimes occurs in the skin lesions."

The "wire-loop" appearance, due to a peculiar hyaline thickening of the walls of the glomerular capillaries, was first described by Baehr, Klemperer and Schifrin,[4] and according to the authors, it does not contain amyloid or lipoid material. Klemperer et al.[28] by using the Mallory connective tissue stain, feel that the "wire-loops" indicate a fibrinoid degeneration and collagenization of the basement membrane. This "wire-loop" appearance is not a constant finding. Mallory [34, 35] was able to find it in only one-half of the cases at the Massachusetts General Hospital. It is interesting to note that Baehr et al.,[4] in speaking about the wire loop appearance, said, "this very characteristic lesion has not been seen by us in any other human diseases, except perhaps eclampsia." It resembles the glomerular and vascular lesions described by Wadsworth [36] in horses which have been immunized by repeated intravenous injections of live bacteria, especially of the pneumococcus and streptococcus group. Klemperer et al.[28] claim to be able to distinguish the "wire-loops" in lupus erythematosus from those occurring in eclampsia, renal amyloidosis, and malignant nephrosclerosis. However, they state that the morphologic aspects of fully developed vascular necrosis obtaining in accelerated arteriosclerosis and in lupus erythematosus are indistinguishable.

Hypertension is relatively uncommon according to Baehr and his associates,[4] whereas Rose and Pillsbury [10] found hypertension present in approximately one-third of their cases.

Miscellaneous: (a) *Eyes:* Intra-ocular lesions are common and assume no definite pattern. Maumenee [37] points out that clinically and pathologically the white fluffy exudates do not differ from those of hypertensive retinitis. Both exudates are made up of cytoid bodies. Histologically, he found that the small superficial retinal hemorrhages were neither related to the larger retinal vessels nor to the white spots but were located in the nerve-fiber layer of the retina. The lesions are not necessarily associated with renal disease because the blood pressure is usually normal, nor are they related to bacterial embolic phenomena because the blood cultures are for the most part sterile. The evidence points to the lesions being local in origin and representing but one of the manifestations of a systemic disease. Keil [24] claims that papilledema is more common than is generally suspected. He attributes the papilledema to vascular damage, "with the transudation of edematous fluid in relation to the papilla."

Even though there may be rather extensive changes in the fundi, patients rarely complain of visual disturbances, such as blurring.

(b) *Central Nervous System:* The marked irritability, the clouding of the sensorium, delirium, stupor, and unconsciousness observed in some patients point to cerebral involvement. On the other hand, some patients remain mentally clear to the end. Tremaine[20] recorded the occurrence of adhesive meningitis in a single case. Keil[24] observed an instance of chronic meningoencephalitis. Jarcho,[38] in his case 5, described many of the cerebral vessels containing thrombi. Areas of distinct encephalomalacia were present in the cortex and the cornu ammonis. There were no vascular lesions in the eyegrounds. Blood cultures were sterile and even though the patient had verrucous endocarditis, there was no bacterial endocarditis. Lobar pneumonia was the terminal complication.

(c) *Lymph System:* Lymphadenopathy is common and it may precede the appearance of the skin lesions. Keil[24] says that the lymphadenopathy in acute lupus sometimes becomes as marked as that in tuberculosis. Goeckererman's[39] treatment of irradiation of the deep gland-bearing areas is evidently based on a belief that all the deep glands are involved. Mallory[25] speaks of a great increase in blood vessels and necrosis of the germinal centers in the lymph glands. Ginzler and Fox[11] first noted the occurrence of peculiar lesions in the lymph nodes and spleen. Microscopically the lymph nodes showed "distinctive areas of focal necrobiosis with or without peculiar hematoxylin-staining bodies"; the spleen showed "periarterial areas of necrosis of the follicular lymphoid tissue, periarterial fibrosis and intimal arterial thickening." Splenomegaly is uncommon.

Etiology: The cause of acute disseminated lupus erythematosus is still a matter of much speculation. At the present time, there are essentially three schools of thought concerning the etiology. One group, predominantly German, believe that the disease is associated with tuberculosis in most instances. A second group, mostly English, feel that it is due to a septicemia probably of the streptococcus. The third group, notably the Americans, favor the varied etiology (mostly toxic).

For a long time many authors regarded this disease syndrome as a manifestation of tuberculous infection or as an allergic response to tuberculotoxin. Goeckerman,[39] Reitmann and Zumbusch,[40] and Low, Logan and Rutherford[41] reported cases in which the lymph glands were extensively involved. Keefer and Felty,[8] in one of their cases, made an inoculum from a lymph gland which showed no histologic lesions characteristic of tuberculosis. They, then, injected the substance into the testes of a rabbit from which a human strain of tubercle bacilli was recovered. Unusual sensitiveness to tuberculin was noted by Ravogli[42] who had two patients die after the cutaneous injection of 0.001 mg. of tuberculin. Keil,[43] from an exhaustive study, concludes "that the occurrence of tuberculosis in cases of lupus erythematosus is coincidental and unrelated."

An infectious etiology is suggested by the clinical features of the disease. H. J. Templeton, commenting upon Madden's[12] paper, told of two cases of acute lupus that recovered after a vaccine, which was prepared from the

hemolytic streptococci cultured from the patients' abscessed teeth, was administered intradermally. He stated: "Whether the recovery occurred because of the vaccine or in spite of it I am not prepared to say. I believe some of the cases are streptococcal in origin, and it is possible that desensitizing therapy may be of some value." Various organisms have been recovered from the blood stream but one is inclined to think that these are terminal invaders. Blood cultures are persistently sterile in the great majority of cases. Roxburgh [44] believes "that all cases of lupus erythematosus are the result of a sensitization of the skin to light by toxins of either the tubercle bacillus or streptococcus." O'Leary [45] and Pels [46] also believe that the disorder is due to a toxemia, probably attributable to a bacterial agent. As is well known, the local Shwartzman phenomenon (intense vascular damage) occurs at the skin area previously prepared by injection of bacterial toxin if a small amount of bacterial toxin is injected intravenously 24 hours later. Apitz [47] and also Gerber [48] found that vascular lesions could be reproduced experimentally in various viscera by the repeated intravenous injection of bacterial toxin. Gerber felt that preliminary preparation in some animals with both an intradermal and intravenous injection enhanced the development of systemic vascular lesions.

Pulay [49] and Gennerich [50] were among the first to note the hypersensitiveness of patients with disseminated lupus erythematosus. Pulay thinks that the location of the skin lesions is due to photosensitivity. He attributes the photosensitiveness to any one of the products of metabolism such as glucose, acetone, hemoglobin, urea, lactic acid, hematoporphyrin and tyrosin, and other chemical substances which have been shown to produce photosensitiveness. In cases in which tuberculosis is prominent, he considered the cause to be the sensitizing action of the tuberculotoxins. Ludy and Corson [51] have recently reported the presence of hematoporphyrinuria and of lead in the skin of 15 out of 18 cases observed in Philadelphia; and they believe the disease to be increasing in frequency in this locality. Lewis [52] has pointed out that the cutaneous areas most often affected are those in which the capillaries are of the atonic type (that is, they do not respond normally to the injection of vasoconstrictor substances). Wilson [53] purposely exposed a small area of skin to ultraviolet rays; and almost immediately the patient developed a severe inflamed area that spread to the rest of the body.

Gennerich [50] believes that a sensitizing substance results from the destruction of the lymph glands by an unknown disease. The ferments of the lymphocytes are freed and circulate in the vascular system as foreign proteins which, when subjected to irritation by light, air, and mechanical agents, produce anaphylaxis. He does not think the lymphatic involvement is due to tuberculosis.

The histopathology of the disease appears to be the result of a toxic agent. Keil [54] advances the concept that acute lupus erythematosus disseminatus is a disease of unknown etiology with a vascular predilection chiefly for the capillaries and to a lesser extent, the arterioles and venules.

This would explain the wide variety and variability of visceral involvement and the protean clinical nature of the disease. However, Klemperer et al.[28] in a recent histopathological study of 20 cases of lupus erythematosus disseminatus conclude that the characteristic organic changes, previously considered as heterogeneous, can now be understood as local manifestations of the widespread damage of collagen. They go on to say that "the various concepts of lupus erythematosus as a disease with predominant localization in a single organ or as a diffuse disease of the peripheral circulation can be entertained no longer."

The rôle of the endocrines, especially the ovaries, must at least be considered as a possible contributory or predisposing factor. Certain cyclical variations in ovarian function are often associated with changes in the skin such as flushing and sometimes bleeding from the mucous membranes. Contratto and Levine [29] claim gratifying results following roentgen irradiation of the ovaries.

Therapy: Inasmuch as the etiology is not established, therapy is mostly supportive and symptomatic. Rest in bed and good nursing care are essential.

Search for and eradication of foci of infection and the use of vaccines [12] (autogenous) have their merits, but eradication of foci of infections should never be undertaken during the acute phase (Keith and Rowntree [55]).

Most of the metallic elements are contraindicated because there are commonly present leukopenia and thrombopenia. Fluids not incompatible with the renal condition are important; dextrose, administered intravenously, is sometimes an aid. Blood transfusions have given at least temporary remissions. Salicylates may be given for the fever and arthralgia.

Exposure to any form of actinic therapy is dangerous.[54] However, roentgen irradiation of the ovaries warrants a trial.[29]

Reports vary as to the effectiveness of sulfonamide therapy. So far results have not been encouraging.

CASE REPORT

Case 1. M. E. D., aged 32, a colored housewife, was admitted September 10, 1940, and died October 24, 1940.

Complaint: "Pains in arms and legs for three weeks."

Family History: Irrelevant.

Past History: The patient had always enjoyed good health except for diphtheria, measles, mumps, varicella, and pertussis in childhood and influenza at the age of 16. She had never had any of the other infectious diseases. She had had frequent bouts of sore throats associated with trembling spells, abdominal pains and chills at the age of 12. There was no history of swollen or painful joints. Since then she had had mild exertional dyspnea. She had never had any visual or auditory disturbances prior to the present illness. There was no history of a chronic cough, hemoptysis, or night sweats. The gastrointestinal, genitourinary, menstrual and neuromuscular systems had always been normal. Her habits were exemplary and her development was normal. There had never been any skin eruption until the present illness.

Present Illness: The patient felt well until three weeks prior to admission when she was stricken suddenly with severe, constant aching pains in all her joints, but there was neither redness nor swelling. There were intermittent, sharp, aching substernal pains unrelated to meals and respirations. Associated with the arthritis were marked malaise, anorexia, headaches, vertigo, diplopia and blurring of vision; however, the latter two symptoms gradually disappeared after several days. She felt feverish and had profuse night sweats. During the weeks before admission, she suffered from chilly sensations, trembling of her limbs, nausea, vomiting, frequency and urgency of urination with incontinence, and a moderately severe cough productive of small amounts of blood streaked, rusty sputum.

Physical Examination: The temperature was 102° F., the pulse rate 80, and her respirations 32 per minute. The blood pressure was 125 mm. Hg systolic and 75 mm. diastolic. She was fairly well developed and nourished but appeared acutely ill. The patient was restless and dull mentally.

The skin was quite dry and there was evidence of recent weight loss. There was no rash, excoriation, or abnormal pigmentation. The hair was that of a normal colored female. The bases of the finger nails were slightly puffy and cyanotic.

The bones were normal. There was no tenderness or swelling.

There was no general glandular enlargement. The epitrochlears were bilaterally palpable and two or three glands were felt in each axilla.

Examination of the head revealed nothing abnormal. The optic discs were normal. The arterioles were irregularly constricted and showed A–V nicking. The venules were moderately distended. There were two small linear hemorrhages near each disc. The mouth showed some gingivitis and dental caries. The tongue was pale and there was mild papillary atrophy. The pharynx was clear and the tonsils were not enlarged.

The thorax was symmetrical and well formed. There was diminished expansion of the right lung as compared to the left. The percussion note was resonant anteriorly but there was impairment from the right mid-scapular region down. The breath sounds were clear anteriorly; they were tubular over the right base and there was also a moderate number of fine dry râles. The heart was very little enlarged to the left. The rate was moderate and the rhythm regular. The sounds were of fair quality. The pulmonic second sound was greater than the aortic. A low pitched systolic murmur was heard over the entire precordium.

The abdomen was normal. The spleen was slightly tender and palpable, just below the costal margin. The liver was not felt.

There was no acute joint swelling or tenderness; however, all joints were a little stiff. The muscles were generally tense and moderately tender. Neurological examination was negative except for bilateral sustained ankle clonus and hyperactive deep reflexes. Pelvic and rectal examinations were not done.

Laboratory Examinations:

Blood examination showed: red blood cells 4,200,000 per cu. mm.; hemoglobin 6.5 gm., 45 per cent (Sahli) (normal 14.5 gm., 100 per cent); white blood cells 4,000; sedimentation rate 60/20; volume of packed red blood cells 26. Hematocrit studies: MCV 62 cubic microns; MCH 15.4 micromicrograms; MCHC 25%. Differential count: myelocytes 0 per cent, non-segmented neutrophiles 32 per cent, segmented neutrophiles 60 per cent, eosinophiles 0 per cent, basophiles 0 per cent, lymphocytes 4 per cent, monocytes 4 per cent.

Stained smears showed marked poikilocytosis, anisocytosis, and pallor. No other abnormalities of the red cells were noted. Platelets normal. No abnormal cells. No sickling.

Eagle test was negative on three different occasions.

Blood chemistry: non-protein nitrogen 21 mg. per 100 c.c. on admission to 92 mg. per 100 c.c. three days before death. Total protein 7.3 gm. per cent. A/G ratio

2.6/4.7. Chlorides 290 mg. per cent. NaCl 478 mg. per cent. Cholesterol 130 mg. per cent. Calcium 9.7 mg. per cent. Phosphorus 5.3 mg. per cent. Phosphatase 6.0 Bodansky units. Uric acid 3.2 mg. per cent. Creatine 1.9 mg. per cent. Icterus index 5. Van den Bergh 0.2 mg. per cent, indirect reaction. Formol gel 4 +.

Blood cultures were repeatedly negative. Blood agglutination, tularemia—0, typhoid H—0, typhoid 0—0, paratyphoid A—0, paratyphoid B—0, proteus X 19—0.

Urine was cloudy, yellow. Specific gravity 1.019, reaction acid. Albumin 2 +. Sugar 0. White blood cells 3–4 per high power field. Red blood cells 0. Occasional granular and rare hyaline cast. Bilirubin, negative to trace. Urobilin 4 + to 0. Stool negative. No pathogenic organisms. Sputum examination showed no tubercle bacilli, 72 hour concentrations. Sputum culture showed mixed flora, no organisms predominating.

Spinal fluid was clear; 2 cells/cu. mm. one lymphocyte and one crenated red cell. Pressure normal. Wassermann reaction negative. Pandy negative. Culture showed no growth. Pleural fluid was clear, yellow. Specific gravity 1.020. Cells 510 per cu. mm., mostly lymphocytes, rare polymorphonuclear. Cultures, aerobically and anaerobically were negative. Concentration test for tubercle bacilli was negative. Guinea pig inoculation revealed no tubercle bacilli.

Tuberculin skin tests negative to 1:100 (old tuberculin).

Roentgenogram of chest (9/11/40): Outlines of right side of heart not made out. Left side seems enlarged. Aorta widened. Diffuse denseness over right lower half of lung due to consolidation or fluid. (9/20/40): Changes in both lower lung fields, due to fluid. (10/10/40): Some clearing of right lung field.

Course: On admission the patient had signs of consolidation in the lower right lung and, although the pneumococci present in the sputum could not be typed, she was started on routine therapy of sulfapyridine. Supportive therapy which included intravenous glucose and saline was also given; and on the seventh and ninth hospital days she received transfusions of 450 c.c. of whole blood. The temperature remained elevated from 101° F. to 104° F., and was septic in character. Inasmuch as some observers considered the possibility of a lung abscess the patient was given 0.45 gm. neoarsphenamine on the seventh day and every other day thereafter for a total of six doses. Sulfapyridine was discontinued on the tenth day.

Signs of fluid in the right chest became evident on the nineteenth and again on the thirty-first hospital days. Thoracentesis yielded respectively 700 c.c., and 350 c.c. of clear, straw colored fluid which was bacteriologically negative. The pulmonary consolidation in the right lung persisted and since tuberculin tests of 1:100 on the twenty-fourth day were negative the patient was started on routine sulfathiazole therapy on the thirty-second day in an attempt to combat the septic course.

About the time sulfathiazole therapy was instituted the patient developed a macular rash on the bridge of her nose which extended in a butterfly shape to both cheeks. In two days the rash became exfoliative and spread rapidly to the neck, arms, thorax and limbs. The epithelium of the involved areas desquamated in great sheets. The diagnosis of acute lupus erythematosus disseminatus was then evident. Sulfathiazole was continued for nine days, but it did not alter the rapid, downward course. The patient lost weight very rapidly and became markedly emaciated. The temperature rose very suddenly to 104° F. on the forty-fifth hospital day and she died.

Throughout her hospitalization she had a fine to coarse tremor, muscle tenderness, and moderate stiffness of the joints. The ankle clonus observed on admission gradually disappeared after three weeks. The ophthalmological appearance of the fundi remained unchanged until the dermatitis appeared and then an increasing number of small hemorrhages and exudates appeared in the fundi.

No pleural or pericardial friction rubs were ever heard. The systolic murmur present on admission was not audible several weeks later.

Patient developed an azotemia (non-protein nitrogen 92 mg. per 100 c.c.) several days before death. There was no rise in blood pressure, and examination of the urine revealed no changes other than those previously found.

*Autopsy Findings.** *Anatomical Diagnosis:* Disseminated lupus erythematosus; necroses and scarring in lymph nodes; focal necroses and hemorrhages in spleen with perivascular scars; focal necroses in pancreas; organizing fibrinous pleurisy; hyaline thickening of alveolar walls in lung; focal myocarditis, slight scarring in heart; chronic epicarditis; chronic mural endocarditis with areas of fibrinoid degeneration; healing focal necroses and periportal infiltration in liver; generalized lesions of small arteries; acute splenic tumor; organizing thrombi in ovarian veins and perivesical plexus; subacute nephritis. Purulent bronchitis (slight); unidentified fungus in a small bronchus. Calcified tuberculous focus in lower lobe of right lung; calcified peribronchial nodes; calcified tubercle in spleen. Decubitus ulcer.

Gross Findings. The autopsy was performed six hours after death. The body was that of a slender, fairly well developed, colored female. The skin of the entire body showed fine desquamation. Over the abdomen and left thigh the desquamation was more marked and there was a moderately thickened layer of cornified epithelium. A decubitus ulcer, 4 cm. in diameter, was present over the sacrum. The cervical, axillary and inguinal nodes were palpable but only moderately enlarged.

Serous Cavities: The pericardial cavity contained 60 c.c. of yellowish, slightly cloudy fluid. The pericardial surfaces were smooth but more opaque than usual. There were a few filmy adhesions over both lungs; there was no fluid. Except for thread-like adhesions over the dorsal surface of the liver, the peritoneal cavity showed nothing remarkable.

Heart: The heart weighed 350 grams. It was not dilated. The measurements of the valve rings were within normal limits. The epicardium was more opaque than usual, indicating slight thickening. The surface was smooth. No gross lesions were seen in the myocardium or endocardium. All of the heart valves were grossly normal except the non-coronary cusp of the aortic valve where several tiny spines, apparently fibrous, were attached to the corpus Arantii. The coronary orifices were normal and the vessels not sclerotic.

Lungs: The anterior surfaces of both lungs showed diffuse thickening, of the pleura and a similar change was seen on the posterior surface of the right lung. Most of the thickening was due to fibrous tissue but in places there was slight roughening due to fibrin. Patchy areas in the posterior part of each lung appeared edematous. The larger bronchi contained sticky mucus. There was no gross consolidation. There was a calcified focus, 3 mm. in diameter, in the middle of the right lower lobe. The lymph nodes at the hilum of each lung contained calcified foci.

Spleen: The spleen weighed 170 grams. There were scattered little fibrous tags attached to the capsule. The splenic pulp had a somewhat rusty coloration. The splenic vein and artery were patent, as well as the portal vein.

Liver: The liver weighed 1560 grams. On section it appeared paler than usual; the lobulation was moderately accentuated. The gall-bladder and bile ducts were grossly normal.

Kidneys: The right kidney weighed 240 grams and the left 150 grams. The capsule of each kidney was not adherent. The external surface of the kidney was smooth. Both kidneys appeared pale and swollen. On section the cortical striae were straight but somewhat blurred. The lining of the renal pelves and ureters appeared normal. About each ureter the connective tissue was thicker than usual, including the tissue about the ovarian veins as well. Both ovarian veins contained thrombi. The thrombus material was mainly decolorized and in places hyaline. In the region of the broad ligament on the left the thrombus material was red and apparently fresher.

*Frank B. Kindell, M.D., Chief, Division of Pathology, Baltimore City Hospitals.

Bladder: The bladder was contracted and its lining normal.

Pelvic Organs: The uterus was small. There were a few myomata a few milli-meters in diameter. A cyst, 2 cm. in diameter, containing old blood, was present in the left ovary. The tubes were grossly normal. Around the neck of the bladder there were thrombi in small veins.

Lymph Nodes: The peritracheal nodes were moderately enlarged. Some of them contained well walled-off old caseous foci and a few such lesions were calcified. The lymph nodes around the abdominal aorta and iliac vessels were larger and soft. These on section showed a bulging, somewhat nodular, cut surface. There were a number of little granules visible which suggested follicles, and about some of these there were narrow hemorrhagic zones. Other lymph nodes were firm and rubbery in consistency and on section appeared white and fibrous. The peri-pancreatic lymph nodes and those at the hilum of the liver were moderately enlarged.

The pancreas, adrenals, stomach and intestines were grossly normal. The neck organs showed nothing remarkable. The tonsils were not obtained with the specimen. The femur bone-marrow was moderately hyperplastic. The thyroid and parathyroids showed no gross lesions. There was very little subcutaneous fat. The muscle in the thigh showed nothing. The record contained no mention of the joints which ap-parently were not examined.

Brain: The meninges over the surface of the brain were grossly normal. The vessels at the base were not sclerotic. The dorsal anterior convolutions were dis-tinctly smaller with wider sulci, indicating much more atrophy than one would expect at this age.

On sectioning the brain the ventricles were not enlarged. Throughout the brain, particularly in the white matter, there were minute reddish streaks (this may have been merely pigment from the embalming fluid). In the corpus striatum, particularly the thalamus, there were a number of tiny holes, in the gross like minute cysts. These were probably minute areas of perivascular atrophy.

The hypophysis and pineal showed nothing abnormal.

Microscopic Findings. Heart: There were minute fibrous scars in the myo-cardium. There were loose accumulations of fibrous tissue about fairly numerous small vessels. These were concentric and completely surrounded the vessel. In a few places there were early suggestively granulomatous lesions with mononuclear cells. Occasionally a perivascular lesion extended into the surrounding myocardium and the proliferative fibrous lesion included very shrunken atrophied muscle fibers. Min-ute blood vessels showed a pink-staining material in their walls, sometimes with perivascular mononuclear cells and proliferation of the intimal layer. Others showed largely necrosis.

In the endocardium there were flat little patches of fibrous scar tissue. In some of these there were minute areas, or central-longitudinal streaks, of hyaline necrosis. The diffuse opacity of the epicardium, as seen in the gross specimen, was due to a thickening of the fibrous tissue forming loose bundles of collagenous material. Not infrequently there were little patches of necrosis with a few mononuclear cells. Occasionally one encountered a red-staining, wavy or spiral appearing, coagulation of connective tissue perpendicular to the surface of the heart—"fibrinoid degeneration." There was diffuse but slight infiltration with lymphoid and mononuclear cells.

Lungs: There was an organizing fibrinous pleurisy with very little cellular in-filtration. There were a few polymorphonuclear leukocytes and a few mononuclear cells. Beneath the exudate the pleural connective tissue formed a thin hyaline layer staining deeply with eosin. No bacteria could be demonstrated in the pleural exudate.

In the parenchyma of the lung there was no fresh pneumonia. There were areas of collapsed lung tissue in which mononuclear cells were found in the collapsed air spaces and also in the alveolar walls. In these areas there was a hyaline thickening

of the alveolar walls. Many of these little streaks contained an occasional mono-nuclear cell, suggesting that a former exudate was in process of being incorporated into the alveolar wall. Where the lung was more expanded these hyaline thickenings of the alveolar walls could still be found in numbers and had an appearance very like that of the so-called "wire-loop" lesions described in the kidney in this condition. In part the bronchi were contracted and contained only a little mucus with a few cells. In the same sections other bronchi were normally wide. Only here and there did a bronchus contain a purulent exudate. Stains for bacteria showed a few Gram positive cocci, some of them in polymorphonuclear leukocytes. In one section two minute bronchi contained a purulent exudate and hyphae of a fungus. The mycelium was wide and short and in the hematoxylin and eosin sections seemed to show septa. Other preparations from the same block failed to show this organism, and smears from many bronchi from the gross lung were spread and stained without showing any other of these organisms.

The vessels in the lung not infrequently were the seat of a hyaline necrosis but in only one vessel was anything suggesting a thrombus to be found.

The changes in the alveolar walls of the lungs were not unlike the "wire-loop" lesions described in the kidney and to our knowledge have not been previously mentioned.

Spleen: There was an acute splenic tumor characterized by clumps of cells in the splenic pulp, often about tiny vessels and with the character of plasma cells or cells with lymphocytic nuclei and a basophilic cytoplasm. There were multiple hemorrhages and minute necroses in the splenic pulp. Occasionally there were concentric hemor-rhages about Malpighian bodies. In some instances these showed coagulated blood and organization. There were some perivascular scars and others in intermediate stages suggesting that they were the result of the organization of the hemorrhages mentioned. Many little vessels in the Malpighian bodies were hyaline. There was swelling and hyalinization of the fibrous tissue in the capsule. Multiple minute areas of necrosis with a few polymorphonuclear leukocytes could be found, suggesting that this was the early stage of the process.

Pancreas: The pancreas was well preserved. There were minute areas of necrosis with early scarring. In one such area which was a little larger, there were large swollen collagenous fibers about a small artery and nerve. In the periphery of the pancreas there was a small focus of "fibrinoid degeneration" in the peripancreatic fat, and extending along one of the fibrous septa. In this latter area there were a few mononuclear cells.

Liver: The capsule was not thickened. There were a few small scars extending into the liver beneath the capsule and in these early scars there were swollen and bright red staining collagenous fibers. The periportal spaces showed early scarring with diffusely scattered lymphocytes and less frequent mononuclear cells. In the parenchyma the liver was moderately but diffusely fatty. The lipoid change was mainly periportal but so widespread as to be seemingly midzonal. There were focal lesions in which the liver cells themselves were necrotic. In other tiny lesions the parenchymal cells were gone and mononuclear cells formed a small nodule, suggesting healing focal necroses.

Adrenal: The tissue was well preserved since the cells of the medulla showed good fixation. In the zona glomerulosa the cells were shrunken and the capillaries dilated. Many of the shrunken atrophied cells appeared necrotic. There was a dif-fuse thickening of the capsule, in large part fibrous with areas of "fibrinoid degen-eration." There were fibrous collars about small and medium sized blood vessels.

Kidneys: There was an acute and subacute nephritis and most of the glomeruli showed swelling of the tuft epithelium and interstitial tissue with compression of the capillaries. There were coarse granular precipitates of protein material in some

of the glomerular spaces. Only an occasional glomerulus showed a thin layer of adhesions between the glomerulus and capsule. Here and there were hyaline necroses, usually in the portion of the glomerulus near the entering arteriole. In these instances in which the arteriole was present, some showed early hyaline changes. Here and there were older glomerular lesions with the character of an intercapillary glomerulonephritis. Ring-like thickenings were also present like those of the "wire-loop" lesions, but these were hardly distinguished from the more general interstitial alteration and seemed to be simply a later part of the same process. The small and larger arteries showed little. About some of the small arteries there were adventitial cellular accumulations of plasma and mononuclear cells.

The tubular changes were · more pronounced than the glomerular lesions. In general the tubules were dilated, with low epithelium. There were numerous casts. Loops of tubules everywhere were the seat of hyaline droplet degeneration. Not infrequently in such areas the tubule contained laked red blood cells. In other areas where the cytoplasm was filled with these coarse granules the cells were actually necrotic and there was early regeneration. Here and there shrunken groups of tubules contained deep red staining small casts and in the interstitial tissue there were lymphocytes and plasma cells and a suggestion of very early scarring.

In those sections which showed the renal pelvis, the interstitial epithelium was normal except for slight autolytic changes and there was no pyelitis.

Bladder: The bladder appeared contracted. Despite the contraction and natural thickening of the submucosa, it still seemed fibrous and scarred. There was no evidence of a chronic cystitis. In the bladder wall a small artery had a hyaline necrosis of its intimal layer with fragmentation of cells and a slight inflammatory reaction.

Uterus: There was atrophy of the uterine mucosa and there were multiple minute hemorrhages. The lower layer had a number of glands, whereas in the superficial half of the uterine lining there were only a few tubular glands approaching the surface. In the uterine wall the vessels were greatly thickened. The intima in such cases showed a hyaline thickening and also an obliterative endarteritis which was more like that found in the uterus in a person of 60 to 80 years than in one 32 years of age. These vessels showed thick hyaline layers in the intima. In other vessels the intima was fibrous and many of the small arteries showed an intact intimal and medial layer with a broad zone of hyaline change about them. Even the uterine muscle appeared atrophied, and there was a diffuse hyalinization.

Ovaries: There was a hemorrhagic cyst in one ovary with early organization of the blood clot. In the margin there were no definite lutein or follicular cells which were recognizable. Nearby there was a smaller cyst with a fibrous organizing layer in the periphery and a great deal of hemosiderin pigment. In this same section there was a well developed follicle in an intermediate stage of maturation.

Ovarian vessels: The sections across the ovarian vessels containing thrombi showed veins containing thrombi in all states of organization. The vessel walls showed proliferative changes but no definite alterations that could be considered the result of inflammation. Many small arteries had very thick hyaline bands in the position of the internal elastic lamella overlaid by a proliferative change in the intima. Some of these vessels showed an infiltration of mononuclear cells in the adventitia and media.

Fallopian Tube: There was a chronic salpingitis with adhesions between the papillary projections of the folds. In some of these there were small hemorrhages.

Pharynx: In the sections of the pharynx there was only a slight round and mononuclear cell infiltration in the submucosa. The epithelial layer was intact. In one of the sections a microscopic lesion was found in which there was a dense hyaline change in a group of collagenous fibers.

Thyroid and Aorta: The aorta itself was normal. As part of the section the pleural and subpleural tissue was present. Here there was a zone of granulation tissue with only a few polymorphonuclear leukocytes and many plasma and mononuclear cells.

Lymph Nodes: There were nine blocks from representative lymph nodes, both the peripheral and internal groups. In all the nodes the solitary follicles had practically disappeared. The lymph cords and sinuses were inconspicuous. Sometimes throughout the whole node, and in all of them in patchy fashion, there was an increased vascularity and these tiny vessels were thickened. In some places the capsule was thick and fibrous and often bands of cellular connective tissue extended into the node. About numerous small vessels there was what appeared to be new-formed cellular connective tissue around the group of vessels, and this was infiltrated with mononuclear cells. Fresh necroses were present in half the sections. These varied in size from microscopical areas to the largest which was 5 mm. in diameter. In the necrotic areas the cells and nuclei were fragmented. The larger of these lesions were not unlike the fresh suggestively caseous lesions of tularemia. In one node the lesion extended to the periphery where the capsule was involved in an inflammatory lesion. Here there were accumulations of polymorphonuclear leukocytes, mainly mononuclear cells, and in small areas the capsular tissue was necrotic. There was inflammation in the fat about the node. Distended lymphatics contained leukocytes. Small vessels, both lymphatics and arteries, showed an interstitial and perivascular inflammatory lesion. The cells present here were plasma and mononuclear cells.

Several of the nodes showed considerable hemosiderin pigment in phagocytic cells. No tubercle bacilli nor bacteria could be demonstrated in the necrotic lesions.

Skin: Five blocks were prepared from representative portions of the skin lesions. Microscopically all showed similar changes. There was a very thin layer of epithelial cells. The keratinized layer on the surface was not particularly conspicuous, but scaling bits of keratinized epithelium could be found. The papillae of epithelium were small and simplified. There was a good deal of melanin pigment both in the basilar layer of the skin and in the connective tissue just beneath. The subepithelial layer of connective tissue was thicker than usual and lacked its usual loose structure. The fibers were swollen and formed a much more compact network than usual. The deeper layer of coarse collagenous fibers showed nothing unusual. There was practically no inflammatory reaction with the exception of a ring, one to two cells deep, around minute vessels. Some of these little vessels were thickened.

The sweat glands in the sections were normal except for an occasional hyaline thickening of the basement membrane, and in a very few cases a few lymphocytic cells about an isolated acinus.

Bone-marrow: The femur bone-marrow was largely fatty, and there was a considerable degree of the gelatinous change commonly seen in emaciated states. The islands of blood-forming tissue were few and widely scattered.

Brain: In the sections of brain the meninges were normal. There was moderate cortical atrophy with widening of the perivascular spaces. In the pons there were perivascular hemorrhages but no lesions of the vessels themselves. In the basal nuclei there were spaces about the vessels which could well be the minute cyst-like lesions described in the gross. In the lenticular nucleus numerous small vessels had rings of intramural and perivascular granular calcification, a lesion which is not infrequently encountered in all sorts of cases. In this section there was one small area of rather old encephalomalacia.

Eye: A hemorrhage in the retina near the nerve head was present in a section from one eye. In this same section a small vessel external to the sclera was thickened and hyaline. No other lesions were found.

Hypophysis and Pineal: No lesions were found.

Anatomical Comment. In view of the rapid progress of the disease process in this case and the resulting short duration, the autopsy findings present features of great interest. Both early and older lesions are present and, with the exception of a verrucous endocarditis, practically all that have been observed in this condition. The absence of any severe or widespread terminal infection makes it possible to be reasonably certain that practically all the changes observed are part of the disease acute lupus erythematosus disseminatus itself. The slight bronchitis and the small decubitus ulcer were all the infected lesions observed, and death was caused in all probability by nephritis and uremia.

The necroses and inflammatory lesions in the lymph nodes, which in general receive less attention in descriptions of this condition, remind one of the lesions of typhoid fever or tularemia. In this case some of the necrotizing lesions did not involve the whole of the lymph node structure in the area, and it seems plausible that the healing of such lesions would result in the scarred vascularized nodes or portions of a node here found side by side. One is also intrigued by the possibility that the perivascular hemorrhages and necroses in the spleen in their healing and resolution leave as an end result the perivascular fibrous thickenings which are so common in lupus. The necrotic lesions involving lymph nodes, spleen, pancreas and blood vessels with the variety of tissues involved, make it difficult to subscribe to the thesis that the lesions of lupus indicate primarily a disease of collagenous tissue. The foetal hepatic necroses of this case could heal without leaving a recognizable scar and the focal myocardial and pancreatic lesions in the end would appear as nondescript scars.

The peculiar thickenings of the alveolar walls in the lungs in this case suggest the incorporation of an organized exudate into the alveolar wall rather than an interstitial change in the wall itself. A similar but much more localized lesion of this sort can not so infrequently be found in the lungs of persons usually with emphysema and chronic bronchitis and patchy pneumonia, in whom all stages in the organization of an intra-alveolar exudate and the apparent fibrous thickening of the alveolar wall can be observed. Probably these eventually practically disappear.

In a disease which so regularly shows some degree of damage to the kidney clinically and definite lesions at autopsy, the active nephritis shown in this instance is not surprising. The "wire loop" lesions, although present here, are not so conspicuous as pictured in other cases, and in any event are obscured by the more general changes. It seems reasonable to assume that they are the result of former minimal lesions.

The autopsy findings furnish no clue to the etiology of the disease, but the picture as a whole as it is present in this case would suggest some as yet undiscovered infectious agent.

CASE REPORTS

Case 2. M. C., aged 38, a white housewife, was admitted February 25, 1938, and died March 5, 1938.

Complaint: "Skin rash for one month."

Family History: Father had eczema and one sister had "skin trouble" for 10 years, presumably eczema.

Past History: The patient's general health had been fairly good. She had had varicella, measles, mumps, pertussis, and diphtheria in childhood without apparent sequelae. She denied other infectious diseases. In November 1933 she was seen in the Psychiatric Clinic of the University of Maryland Hospital, and it was the impression of those who saw her that she was "intellectually and emotionally weak" and that "her reaction type was that of a poorly organized hysteria." Therefore, little credence could be placed in some of her answers. She was subject each winter to frequent head-colds which were accompanied by very little malaise, fever, and sore throats. The visual and auditory senses had been normal prior to her present illness. In 1932 she had all of her teeth extracted because of "extreme decay and abscesses." She denied a chronic cough, hemoptysis, night sweats, and pain in the chest. She had had exertional dyspnea and palpitation for a number of years, but no ankle edema, or nocturnal paroxysms. Her gastrointestinal system had been essentially normal except for chronic constipation and occasional bleeding attributed to hemorrhoids. Urinary function had always been adequate and symptom-free. The catamenia had been normal up to 1936 when she began to have some menorrhagia and metrorrhagia and a feeling of heaviness and numbness in her pelvis. A supravaginal hysterectomy was done at the West Baltimore General Hospital because of uterine fibromata and endometrial hyperplasia. She had had three normal pregnancies previous to 1936. The neuromuscular system was significant only in the fact that she had always "fainted" at the slightest provocation. Her habits were excellent. She had had no skin rash prior to the present illness.

Present Illness: The onset of the patient's present illness actually occurred in March 1937 when, for the first time, she noticed a "red spot" on the center of her forehead. The lesion was approximately 4 cm. in size and got no larger. There was no history of the lesion scaling, oozing, itching, or burning. However, one month later she became more concerned about it, presumably for cosmetic reasons. She consulted her family physician who told her the lesion was "ring worm" and gave her some salve to apply. Soon thereafter similar lesions appeared on the cheeks, nose, and right side of the forehead. She then consulted another physician who advised her to spend most of the time in the sunshine. She followed his advice and the lesions spread to the neck and shoulders; at the same time her hair began to fall. out in great quantities. As she was obviously getting worse she returned to the physician several months later (during the summer) and he gave her five or six "light treatments" which caused the lesions to spread further over the face, neck, and shoulders and to burn and itch. The treatments were discontinued and the patient was placed on a special diet free from meats and eggs, and all fruits except bananas. She remained on this diet until admission. She got along fairly well during the rest of the summer and fall except for general malaise, nervousness, and weakness. Her skin lesions cleared only slightly, but the alopecia became so marked by January that she went to the University of Maryland Hospital Skin Clinic. The diagnosis of lupus erythematosus was made and she received a course of Bismuth Salicylate 0.2 gm. each week for five weeks. The day following the last injection (February 2, 1938) there was a marked exacerbation of her skin lesions which became "fiery" red and began to spread to the arms and chest. Two days later the entire body was involved. The skin became slightly edematous. There was some oozing and much

scaling. There was marked malaise, weakness, and fever. She stated that during the two months before admission she had lost at least 20 pounds.

Physical Examination: The temperature was 102.2° F., the pulse was 100, the respirations were 20, and the blood pressure 100 mm. Hg systolic and 40 mm. diastolic. The patient was an undernourished and poorly developed woman whose age was difficult to approximate by inspection. She was mentally alert and coöperative.

The entire skin of the body was covered with confluent, erythematous, vesicular, scaling lesions. The skin was warm, tender and it blanched with pressure. The scaling was most marked on the head, neck, arms, hands, and thorax. The lower portion of the legs was covered with loose skin under which there appeared to be a small amount of serum. The feet were covered with large papules interspersed with apparently normal skin. There was almost complete alopecia and the remaining hair was very fine in texture.

The bones were normal. There was no tenderness or swelling.

The cervical and epitrochlear glands were not felt. There were a few, medium-sized, discrete, non-tender glands in the axillae. The inguinal glands were also discrete and slightly enlarged.

There was excessive lacrimation of the eyes. The lid margins were reddened. The pupils and extraocular movements were normal. The fundi showed many small areas of whitish exudate with several larger ones above and below the left disc. There was no apparent papilledema. The skin lesions extended into the auditory canals but the drums were normal. The mouth revealed complete adentia and an ulcer on the lower left anterior portion of the gum. The pharynx was not injected. The tonsils were normal in appearance.

The thorax was not remarkable. The breasts were small, underdeveloped and contained no masses or tenderness. The lungs were resonant throughout. No abnormal sounds were heard. There were no râles. The heart was not enlarged to the left or right. The rate was moderately fast, the rhythm was regular. The sounds were of good quality. A soft systolic murmur was audible over the entire precordium.

The abdomen was scaphoid. A midline scar extended from the umbilicus to the symphysis pubis. The liver and spleen were not felt. There was no fluid, abnormal masses, or tenderness.

There was no joint tenderness or swelling. Neurological examination was normal except for hyperactive reflexes and absent abdominal reflexes.

Pelvic examination revealed a small normal cervix. The fundus and adnexae were not felt. There were no masses or tenderness. Rectal examination was normal.

Laboratory Examinations: Blood examination showed: red blood cells 3,500,000 per cu. mm.; hemoglobin 72 per cent (Sahli) (normal 14.5 gm. 100 per cent); white blood cells 1,000 to 3,850.

Differential Count:

	2–26–38	3–3–38
Myelocytes	7%	0%
Non-Segmented neutrophiles	20%	11%
Segmented neutrophiles	43%	37%
Eosinophiles	1%	9%
Basophiles	0%	0%
Lymphocytes	27%	40%
Monocytes	2%	3%

Stained smears showed no abnormality of the red blood cells except pallor. The platelets were normal. No parasites seen. Eagle (blood serology) test negative.

Blood chemistry: Non-protein nitrogen 29 mg. per 100 c.c.; sugar 118 mg. per 100 c.c.; total protein 6.1 gm. per cent; A/G ratio 3.7/2.4; chlorides 265 mg. per cent; NaCl 437 mg. per cent; cholesterol 110 mg. per cent; calcium 7.8 mg. per cent; phos-

phorus 3.1 mg. per cent; icterus index 3; Van den Bergh 0.1 mg. per cent (indirect reaction).

Blood cultures: (3–2–38) *Staphylococcus albus* (hemolytic), 100 colonies per c.c. (3–3–38) *Staphylococcus albus* (hemolytic). Cultures presumably contaminated by the skin which could not be prepared adequately.

Urine cloudy, yellow. Specific gravity 1.020; reaction acid; albumin, 0 — 2 +. Sugar 0. Occasional white blood cell. Occasional red blood cell. Casts — 0. Stool negative.

Pleural fluid (3–4–38) clear, straw colored, 300 c.c. Cells: 25 polymorphonuclears. Culture negative. Protein 11 gm. per cent. (3–5–38) 250 c.c. grossly bloody fluid. Culture negative.

Roentgenogram of chest (portable) (3–3–38) showed dense clouding at the right base, probably due to fluid.

Course: The patient was given a high caloric and high vitamin diet supplemented with cevitamic acid and vitamin B. The skin was treated with olive oil and later with calamine liniment and carron oil. The lesions improved markedly; there was more scaling and evidence of progressive epithelization with healing.

The temperature on admission rose from 102.2° F. to 103.4° F., and remained elevated and septic in character until the sixth hospital day when it leveled off and remained about 100° F. until death three days later. Salicylates started on the fourth hospital day had no effect.

On the seventh hospital day she suddenly became dyspneic and examination revealed signs of fluid at the right base. A thoracentesis yielded 300 c.c. of clear fluid. There was improvement in her dyspnea. She was given a second transfusion (550 c.c.) and developed a mild reaction. However, signs of cardiac insufficiency became evident and she was rapidly digitalized. A thoracentesis done on the ninth hospital day yielded 250 c.c. of bloody fluid. That afternoon the patient died without much change in her condition.

Case 3. C. L., aged 33, a colored housewife, was admitted August 8, 1940, and discharged October 7, 1940.

Complaint: Multiple joint pains for three months.

Family History: Mother died in a mental sanatorium. One sister died in a tuberculosis sanatorium.

Past History: The patient had always enjoyed good health until the present illness. She had had only the usual childhood diseases without sequelae. She had been subject to frequent sore throats until 1932 when her tonsils and adenoids were removed. There was no history of other infectious diseases. There were no visual and auditory signs or symptoms. She denied a chronic cough, sputum, night sweats, and hemoptysis. The cardiac, gastrointestinal, urinary and neuromuscular systems were negative. Her catamenia was normal. Following a miscarriage in 1925 she had had a tubo-ovarian abscess. A right salpingo-oöphorectomy, excision of corpus luteum cyst of the left ovary, and an appendectomy were performed at the University of Maryland Hospital. She had had no skin lesions prior to her present illness.

Present Illness: The patient was well until May 1940 when she developed slight pain and stiffness in her fingers. About the same time she noticed stiffness in the anterior portion of the thighs, especially when walking up and down stairs. The stiffness in the hands disappeared within two weeks but that in the thighs persisted. It seemed to be worse in the mornings, but quickly improved after arising. There was no history of chills or fever. She continued to take one white tablet before meals and one green tablet after meals until admission without apparent relief.

Approximately one month later she noticed minimal pigmentation and roughness of the skin over the bridge of the nose and the point of the chin. The lesions dis-

appeared from the face within two weeks but similar lesions appeared on the left breast, in the left axilla and on the left shoulder.

She experienced marked malaise, anorexia and weight loss of approximately 30 pounds.

Physical Examination: The temperature was 100° F., the pulse rate 110, and the respirations 20 per minute. The blood pressure was 105 mm. Hg systolic and 70 mm. diastolic. The patient was a fairly well developed and nourished colored woman who appeared her stated age and who was in no obvious discomfort.

The skin was warm and rather dry. There was an area of slightly increased pigmentation over the bridge of the nose. On the chin there was an area of increased pigmentation with several papules about 2 mm. in diameter. An area two to three inches in diameter was present on the left breast. This lesion was dry, scaling and had increased pigmentation. There were similar lesions at the insertion of the left deltoid muscle and along the left posterior axillary line.

The bones were normal except for suggestive fusiform swelling of the phalanges. All joints were supple and free from pain.

There was no local or general glandular enlargement.

The eyes were perfectly normal to external examination. The fundi showed rather large (½ — 1 D.D.) dull, white areas which were unlike exudates usually seen in arteriolar disease. They were not fluffy and were generally situated between an artery and vein; however, occasionally a vessel was partially covered. Most of the exudates were within 2 disc diameters of the disc. A few hemorrhages were present. No Rothe spots were seen. The discs and vessels appeared normal. The ears, nose, mouth, and pharynx showed no abnormalities.

The breasts were not tender and contained no abnormal masses.

The thorax was well formed and symmetrical. Expansion was equal and adequate. The lungs were perfectly clear to percussion and auscultation. The heart was slightly enlarged to the left and right. The sounds were of good quality. There was a soft systolic murmur heard over the entire precordium. The rate was moderately fast and the rhythm was regular. No friction sounds were audible.

The abdomen was scaphoid. A midline incision scar extended from the umbilicus to the symphysis pubis. The liver edge extended just below the costal margin. The spleen was not palpable. No abnormal masses or tenderness were elicited.

Pelvic examination was normal except for absent right adnexa. No ulceration of mucosa. Rectal examination was negative and confirmed the pelvic examination.

Neurological examination was perfectly normal.

Laboratory Examinations:

Blood examination showed: red blood cells 2,630,000 per cu. mm.; hemoglobin 8.5 gm., 52 per cent (Sahli) (normal 14.5 gm., 100 per cent); white blood cells 2,480; sedimentation rate 68/20; volume packed red blood cells 22.

Hematocrit studies: MCV 85 c.μ, MCH 32 micromicrograms, MCHC 33%.

Differential Count:

	8/8/40	8/23/40
Myelocytes	4%	0%
Non-segmented neutrophiles	1%	7%
Segmented neutrophiles	75%	77%
Eosinophiles	0%	1%
Basophiles	0%	0%
Lymphocytes	17%	12%
Monocytes	3%	3%

Stained smears showed moderate anisocytosis and poikilocytosis. There were no polychromatophilia, stippling, or nucleated red blood cells. No parasites were seen. No sickling. Fragility test normal. Reticulocytes 1.0 per cent. Platelets 1,300,000,

normal appearance. Bleeding time 45 seconds. Clotting time 2 minutes 15 seconds. Clot retraction 1 hour 30 minutes. Sternal puncture normal. Eagle test negative.

Blood chemistry: nonprotein nitrogen 24 mg. per 100 c.c. (8/8/40). Total protein 7 gm. per cent (8/28/40); 4.7 gm. per cent (9/20/40). A/G ration 2.6/4.6 gm. per cent (8/28/40); 2.3/2.4 gm. per cent (9/20/40). Cholesterol 240 mg. per cent. Uric acid 4.8 mg. per cent. Icterus index 5. Formol gel 4+. Blood culture negative. Blood agglutination for *B. abortus*, Melitensis, suis, 0.

Urine cloudy yellow. Specific gravity 1.006, 1.018, 1.014, pH acid. Albumin 2+, 0. Sugar 0. White blood cells 3-8 per high power field. Occasional red blood cell and granular cast. Culture: *B. subtilis*. Fishberg concentration test (8/12/40), specific gravity 1.010 (1 hr.), 1.008 (2 hrs.), 1.010 (3 hrs.). Phenolsulphonphthalein excretion: (15 min.) 0, (1 hr.) 20, (30 min.) 25, (2 hrs.) 0, total 45 per cent. Stool negative. Basal metabolic rate — 1.

Biopsy of skin showed some edema of subcutaneous connective tissue and slight evidence of chronic inflammation. No specific lesions. Excision of cervical lymph gland—normal. Electrocardiogram showed normal mechanism. Roentgenogram of chest, heart and aorta normal. Lungs clear. Hips and pelvis—nothing abnormal seen.

Course: The patient was placed on the regular hospital diet and bed rest. Her complaints were never acute. The skin lesions remained unchanged. A biopsy of the skin showed some edema of the subcutaneous tissue and slight evidence of chronic inflammation but no specific lesions. The arthralgia gradually disappeared without specific therapy. Soon after admission she rapidly developed ideas of reference and persecution which grew progressively worse. Finally on August 20, 1942 she prevailed upon her husband to take her home against the will of the attending physicians. Two days later she was admitted to the psychiatric division in a mental state of confusion and partial disorientation with hallucinations and suicidal attempts. Her course on the psychiatric wards was uneventful and short. Dr. Esther Richards thought the patient had a delirium, and it was the impression of the house staff that the delirium was dependent upon toxic factors probably associated with the lupus. Dr. A. E. Maumenee of the Wilmer Institute at Johns Hopkins Hospital saw the patient, and he said that perhaps the same pathological process occurred in the brain as in the eye grounds; that is, a swelling of the neuroglia fibers. It is of significance to note that the mental state cleared up as the exudates in the fundi became fewer in number, smaller and more grayish. The patient was transferred September 17, 1940 to the medical service for further study. Physical examination was the same except for slight general glandular enlargement. The left cervical glands later became prominent and slightly tender. One of these lymph nodes was removed for biopsy but it showed no abnormality. As the glandular enlargement progressed the skin lesion of the nose became puffy and dusky red and spread to the malar eminences back to ears and to the forehead. The line of demarcation was sharp. The lesions elsewhere on the body showed little change. A few fresh hemorrhages appeared in each fundus, but there was no increase in number or size of the exudates.

The temperature was only moderately elevated and ranged from 99° F. to 100.5° F. The blood picture remained essentially unchanged. There was a persistent albuminuria. The patient continuously asked to go home and inasmuch as she was getting no worse it was decided to let her go home on October 7, 1940. One month later the patient died from a fairly acute illness without hospitalization.

Case 4. D. R., aged 18, a white girl, was admitted June 24, 1940, and died February 18, 1941.

Complaint: Pain and swelling of the joints of six months' duration.

Family History: Father and mother died at 59 years of asthma (probably cardiac) and "neuritis."

Past History: The patient had had only the usual childhood diseases which were uncomplicated. At the age of 12 she had an "attack of rheumatism" about which she remembered little except that she was placed at bed rest for three months under a doctor's care. She knew of no complications that might have occurred at that time and stated that no restrictions were placed on her activity following this attack. She was advised to have her tonsils and adenoids removed but this advice was rejected. She had never had any visual or auditory symptoms. There was no history of chronic cough, hemoptysis, or night sweats. The gastrointestinal, genitourinary, menstrual, and neuromuscular systems had always been normal. Her development was normal and her habits were excellent. There had never been any skin eruption until the present illness.

Present Illness: At Christmas time, 1939, the patient had a sore throat and began to suffer with fleeting pains in her joints with redness and swelling. At this time, too, she noticed for the first time a "scabby" skin eruption about her eyes that progressed to include her cheeks as well. She did not seek medical aid but treated herself by alcohol rubs and short periods of rest when incapacitated. During the next six months, the joint pains separately and fleetingly involved the knees, ankles, feet, shoulders, elbows, wrists, and hands. The skin eruption cleared somewhat on the face but spread to involve the lower arms and legs. The day prior to admission she had an acute flare-up of her joint manifestations which were so severe that she was unable to get relief.

Physical Examination: The temperature was 100° F., the pulse rate 90, and respirations 26 per minute. The blood pressure was 134 mm. Hg systolic and 84 mm. diastolic. She was a well developed and nourished red-haired white female who appeared her stated age. She lay in bed in rather acute distress and was obviously unwilling to move.

The skin was hot and dry, and generally clear except for comedones and the following lesions. At the outer canthus of each eye and in a very imperfect "butterfly" area over the bridge of the nose and upon the cheeks were red, scaly, dry, maculopapular areas with indefinite borders. Similar larger patches appeared upon the extensor surfaces of the forearms and lower half of the upper arms and lower anterior surfaces of the legs.

The bones were normal. There was no tenderness or swelling of the bones.

There was no general glandular enlargement.

Examination showed the head to be perfectly normal. There was no alopecia or lesions of the scalp. The eyes were completely negative except for very moderate tortuosity of the retinal arteries. The ears and nose were normal. The mouth was negative except for dirty, carious teeth. The pharynx revealed small uninflamed tonsils. There were many enlarged lymph nodes in the anterior cervical triangles.

The thorax was symmetrical and well formed. The breasts were normal and virginal. The lungs were perfectly clear to percussion and auscultation. The heart was full sized, globular, but otherwise negative. No murmurs were heard.

The abdomen was normal except for slight tenderness to deep palpation over the left kidney region. The liver and spleen were not felt.

Pelvic organs were those of a normal virginal female.

The extremities revealed the skin lesions as described above. There were swelling, tenderness and pain on motion at both wrists and the left elbow. There was some local heat but no redness. The left foot was arched acutely and fixed. The neurological examination was normal except for generalized hyperactivity of the deep reflexes.

Laboratory Examinations:

Blood examination showed: red blood cells 4,270,000 per cu. mm. Hemoglobin 12.5 gm., 88 per cent (Sahli) (normal 14.5 gm., 100 per cent). White blood cells

6,150. Sedimentation rate 32 mm. (corrected). Volume of packed red blood cells 40 c.c. Hematocrit studies: MCV 93 c.μ, MCH 29 micromicrograms, MCHC 31%. Differential count: myelocytes 0 per cent, polymorphonuclears 74 per cent, eosinophiles 0 per cent, basophiles 0 per cent, lymphocytes 23 per cent, monocytes 3 per cent. Stained smears appeared normal. No abnormal cells seen. No parasites. Wassermann reaction negative. Kline screen test doubtful.

Blood chemistry: nonprotein nitrogen 28 mg. per 100 c.c. Sugar 87 mg. per 100 c.c.

Urine, yellow. Specific gravity 1.020, pH acid. Albumin 0. Sugar 0. White blood cells 0. Red blood cells 0. Casts 0. Phenolsulphonphthalein 25 per cent in one hour.

Kidney function tests were unsatisfactory because of patient's inability to cooperate, but all specimens ranged between 1.003 and 1.020 in specific gravity. A heavy trace of porphyrin was found in the urine by chemical analysis.

Stool negative. Electrocardiogram showed normal tracings in Leads I, II, and III, and notching of T in Lead IV. Teleroentgenogram revealed a globular heart and clear lung fields without evidence of pericardial or pleural change. The joints showed no changes from normal.

Course: The patient was placed on salicylates with dramatic relief of her joint symptoms but no effect on the erythema. When salicylates were discontinued without the patient's knowledge, the joint pains returned and the salicylates had to be started again. During her stay in the hospital, the patient's appearance was so suggestive of acute lupus erythematosus disseminatus that investigations were carried out along this line. Ultraviolet ray sensitivity was tested over the skin of the abdomen showing a marked erythema without vesiculation after exposure for 10 seconds and moderate erythema after as short a time as five seconds. A skin biopsy from one of the areas of erythema produced by ultraviolet ray showed changes consistent with chronic inflammation including perivascular round cell infiltration. All skin lesions gradually disappeared. Biweekly sedimentation rate determinations remained consistently between 32 and 36 mm. corrected. She continued to have slight (to 99.2° F.) fever. After 60 days of bed rest, a tonsillectomy and adenoidectomy were performed under general anesthesia. Recovery was uneventful. Feeling that nothing further could be done for the patient, and that a gain of five pounds in weight was a sign of satisfactory progress, she was discharged on August 17, 1940 as improved with instructions to follow a rest régime at home and to report back for observation.

She was subsequently seen on September 7, 1940 (one month after discharge) at which time she had no complaints. The urine was negative and the sedimentation rate was 32 mm. (corrected). She was again seen November 14, 1940 (three months after discharge) at which time her urine was still negative. Red blood cells 3.63; hemoglobin 57 per cent; white blood cells 6,700; polymorphonuclears 74 per cent; lymphocytes 19 per cent; eosinophiles 3 per cent; monocytes 4 per cent; sedimentation rate 27 mm. (corrected); volume index 98; mean corpuscular volume 85.1 cμ.

Five weeks prior to her second hospital admission February 17, 1941, the patient was forced to remain constantly in bed, largely because of weakness. During this time she had several attacks of pain in her left flank. She said she had seen several small red spots over her body and arms. There had been no hemoptysis. On the date of admission, she had substernal pain and while on her way to the bathroom, she "fainted" and because of this was brought to the hospital.

Physical Examination: The temperature was 100.2° F., the pulse rate 128, and the respirations 42 per minute. The blood pressure was 110 mm. Hg systolic and 72 mm. diastolic. She showed evidence of weight loss and was obviously critically ill. She was extremely dyspneic and orthopneic. Respirations were rapid and shallow. The skin was very pale, and there were no petechiae or eruptions of any kind. Mucous membranes were also pale but were otherwise negative, except for two pe-

techial hemorrhages in the right lower conjunctival sac. Ophthalmoscopic examination was negative. There was slight engorgement of the neck veins. The cervical glands were not enlarged.

The lungs were clear except for occasional moist râles at both bases. Examination of the heart showed a double apical impulse. There was a systolic thrill at the apex. The heart was moderately ·enlarged to the left. The sounds were of poor quality. At the left border of the sternum, there was a protodiastolic gallop. There was a soft systolic murmur at the apex and some observers noted a low-pitched mid-diastolic rumble just inside the apex. Pulses were equal at the two wrists. Examination of the abdomen was unsatisfactory because the patient could not lie down owing to the marked dyspnea and orthopnea. The liver was probably two fingers' breadth below the costal margin. The spleen was not felt. The inguinal glands were small and rubbery.

There was no edema of the extremities. Slight cyanosis was perceptible in the nail beds.

Laboratory Examinations:

Blood examination showed: red blood cells 3,280,000 per cu.mm. Hemoglobin 8 gm., 58 per cent (Sahli) (normal 14.5 gm., 100 per cent). White blood cells 19,850. Differential count: myelocytes 0 per cent, non-segmented neutrophiles 2.5 per cent, segmented neutrophiles 88 per cent, eosinophiles 1 per cent, basophiles 0 per cent, lymphocytes 7.5 per cent, monocytes 1 per cent. Stained smears showed moderate anisocytosis and poikilocytosis of the red blood cells with central achromia. Platelets were abundant. Blood culture was negative.

Course: The patient was given digitalis and morphine, but she became rapidly worse and died 14 hours after admission. Permission for an autopsy could not be obtained.

COMMENT

These four cases were selected primarily because they illustrate some of the variable clinical manifestations of acute lupus erythematosus disseminatus.

The skin lesions in case 1 did not appear until almost two months after the onset of the present illness which was characterized by polyarthritis, marked malaise, anorexia, fever, night sweats, and signs of nephritis. Two weeks after hospitalization the patient was tested with old tuberculin 0.1 c.c. in dilutions of 1 : 1,000,000; 1 : 100,000; 1 : 10,000; 1 : 2,000; and 1 : 100 over a period of 10 days. It is interesting to note that the skin lesions appeared six days after the last tuberculin injection (0.1 c.c. of 1 : 100) which was negative after 48 hours. Whether or not the tuberculin precipitated the dermatitis is not certain but it is a possibility. Concomitant with the appearance of the skin lesions was the presence of an increasing number of small hemorrhages and exudates in the fundi. Pleural effusion occurred on two occasions, but it was not a prominent feature of the clinical course. The patient developed azotemia (nonprotein nitrogen—92 mg. per 100 c.c.) several days before death. There was no rise in blood pressure or additional urinary changes.

The onset of the present illness in case 2 was marked by the skin eruption. Even though the dermatitis was typical it was not recognized, and the patient was advised by her physician to take sun baths. ·The danger from ultraviolet exposure is clearly illustrated by the increase in severity of the skin

lesions and the general condition. This case also illustrates the deleterious effect of a heavy metal. She received a course of bismuth salicylate 0.2 gm. intramuscularly each week for five weeks. The day following the last injection, there was a marked exacerbation of her skin lesions which became "fiery" red and began to spread to the arms and chest. Two days later, the entire body was involved. Pleural effusion was a terminal event.

It is of significance to note in case 3 that the delirium cleared up as the exudates in the fundi became fewer in number, smaller, and more grayish. One seems justified in postulating that the same process existed in the brain and eyes; namely, a swelling of the neuroglia fibers. Unfortunately, an autopsy could not be obtained. Arthralgia and myalgia preceded the skin lesion by one month; and fresh hemorrhages appeared in the fundi during an exacerbation of the skin lesion, just as occurred in case 1.

The arthralgia and skin lesions occurred simultaneously in case 4. The response of the polyarthritis to salicylates was excellent and when the salicylates were discontinued without the patient's knowledge, the joint pains returned. The electrocardiogram was normal. Even though there was dramatic relief of her joint symptoms with salicylates and there was a history of "an attack of rheumatism" five years previously, the skin lesions were so suggestive of acute disseminated lupus erythematosus that the following investigations were carried out. Ultraviolet ray sensitivity was tested over the skin of the abdomen and showed a marked erythema without vesiculation after exposure for 10 seconds and moderate erythema after as short a time as five seconds. A skin biopsy from one of the areas of erythema produced by ultraviolet ray showed changes consistent with chronic inflammation including perivascular round cell infiltration. The skin lesions gradually disappeared without any specific therapy and they did not recur even during the terminal stages. The appearance of renal damage and anemia occurred very late during the course of her illness. The cardiac murmurs which were heard, for the first time, during her last hospital admission could be explained on the basis of the severe anemia. However, they suggest the possibility of a verrucous endocarditis.

All four of the cases had skin lesions, prolonged fever, leukopenia with secondary anemia, nephritis, and a remittent cachectic course. Cases 1, 3, and 4 had polyarthritis and arthralgia. Cases 1 and 2 had pleural effusions. Case 4 may have had verrucous endocarditis. The duration of the disease in this group of patients ranged from two months to 12 months, the average being approximately eight months.

SUMMARY

A review of the literature on acute lupus erythematosus disseminatus is presented. An attempt is made to emphasize the clinical aspects. Four cases, two colored and two white females, are used to illustrate the variability of the symptom-complex.

Acute lupus erythematosus disseminatus is a disease of unknown etiology associated with widespread visceral lesions predominantly involving the kidneys, lymph nodes, blood vessels, serous and endocardial surfaces, as well as the skin. There is a marked predilection for females in the second and third decades. The prognosis is grave and the average duration of the disease is approximately 18 months. The clinical picture is variable; however, the skin lesions, leukopenia with secondary anemia, arthritis, prolonged fever, and signs of renal involvement are prominent features that should make the diagnosis possible. The avoidance of any form of actinic therapy, except perhaps the roentgen irradiation of the ovaries, and the danger of eradication of foci of infection during the acute phase cannot be overemphasized.

BIBLIOGRAPHY

1. OSLER, W.: The erythema group of skin diseases, Am. Jr. Med. Sci., 1904, cxxvii, 751–754.
2. LIBMAN, E., and SACKS, B.: A hitherto undescribed form of valvular and mural endocarditis, Arch. Int. Med., 1924, xxxiii, 701–737.
3. CHRISTIAN, H. A.: Long continued fever with inflammatory changes in serous and synovial membranes and eventual glomerulonephritis: a clinical syndrome of unknown etiology, Med. Clin. N. Am., 1935, xviii, 1023–1026.
4. BAEHR, G., KLEMPERER, P., and SCHIFRIN, A.: Diffuse disease of the peripheral circulation (usually associated with lupus erythematosus and endocarditis), Trans. Assoc. Am. Phys., 1935, l, 139–155.
5. KAPOSI, MORIZ K.: Neue Beiträge zur Kenntnis des Lupus erythematosus, Arch. f. Dermat. u. Syph., 1872, iv, 36–78.
6. OSLER, W.: On the visceral complications of erythema exudativum multiforme, Am. Jr. Med. Sci., 1895, cx, 629.
7. FORDYCE, J. A.: Lupus erythematosus in a tuberculous subject, Jr. Cutan. Dis., 1899, xvii, 113–116.
8. KEEFER, C. A., and FELTY, A. R.: Acute disseminated lupus erythematosus: report of three fatal cases, Bull. Johns Hopkins Hosp., 1924, xxxv, 294–304.
9. KIERLAND, R. R.: Classification and cutaneous manifestations of acute lupus, Proc. Staff Meet. Mayo Clin., 1940, xv, 376–377.
10. ROSE, E., and PILLSBURY, D. M.: Acute disseminated lupus erythematosus—a systemic disease, ANN. INT. MED., 1939, xii, 951–963.
11. GINZLER, A. M., and FOX, T. T.: Disseminated lupus erythematosus: a cutaneous manifestation of a systemic disease (Libman-Sacks); report of a case, Arch. Int. Med., 1940, lxv, 26–50.
12. MADDEN, J. F.: Acute disseminated lupus, Arch. Dermat. and Syph., 1932, xxv, 854–875.
13. STEWARD, C. C., JR., and GOECKERMAN, W. H.: Lupus erythematosus disseminatus in juveniles, Am. Jr. Dis. Child., 1931, xxxxii, 864–868.
14. REIFENSTEIN, E. C., REIFENSTEIN, E. C., JR., and REIFENSTEIN, G. H.: A variable symptom complex of undetermined etiology with fatal termination, Arch. Int. Med., 1939, lxiii, 553–574.
15. WEIDMAN, F. D., and GILMAN, R. L.: A case of acute disseminated lupus erythematosus; necropsy disclosing acute endocarditis but not tuberculosis, Brit. Jr. Dermat. and Syph., 1931, xxxxiii, 641–647.
16. BELOTE, G. H.: Lupus erythematosus disseminatus: its present status, Arch. Dermat. and Syph., 1939, xxxix, 793–806.
17. STOKES, J. H.: The diagnosis of disseminated erythematosus lupus, Med. Clin. N. Am., 1926, x, 290–299.
18. O'LEARY, P. A.: Disseminated lupus erythematosus, Minnesota Med., 1934, xvii, 637–644.

19. FRIEDBERG, C. K., GROSS, L., and WALLACH, K.: Non-bacterial thrombotic endocarditis associated with prolonged fever, arthritis, inflammation of serous membranes and widespread vascular lesions, Arch. Int. Med., 1936, lviii, 662–684.

20. TREMAINE, M. J.: Subacute Pick's disease (polyserositis) with polyarthritis and glomerulonephritis: a report of two fatal cases, New England Jr. Med., 1934, ccxi, 754–759.

21. SLOCUMB, C. H.: Arthralgia and arthritis of lupus, Proc. Staff. Meet. Mayo Clin., 1940, xv, 683–686.

22. Cabot Case: New Eng. Jr. Med., 1941, ccxxv, 151–155.

23. Cabot Case: New Eng. Jr. Med., 1941, ccxxv, 956–958.

24. KEIL, H.: Dermatomyositis and systemic lupus erythematosus, Arch. Int. Med., 1940, lxvi, 339–383.

25. Cabot Case: New Eng. Jr. Med., 1941, ccxxv, 418–422.

26. DAVIS, D., and AYMAN, D.: Subacute bacterial endocarditis with unusual vesiculobullous skin lesions: necropsy reports in 2 cases, Am. Heart Jr., 1927, ii, 671–681.

27. CORBURN, A. F., and PAULI, R. H.: Quoted by KEIL.[24]

28. KLEMPERER, P., POLLACK, A. D., and BAEHR, G.: Pathology of disseminated lupus erythematosus, Arch. Path., 1941, xxxii, 569–631.

29. CONTRATTO, A. W., and LEVINE, S. A.: Acute lupus erythematosus disseminatus, report of a case, New Eng. Jr. Med., 1939, ccxxi, 602–604.

30. GROSS, L.: Cardiac lesions of Libman-Sacks associated with lupus, Am. Jr. Path., 1940, xvi, 375–408.

31. GROSS, L.: Heart in atypical verrucous endocarditis (Libman-Sacks), Libman Anniv., 1932, ii, 527–550.

32. STICKNEY, J. M., and KEITH, N. M.: Renal involvement in disseminated lupus erythematosus, Arch. Int. Med., 1940, lxvi, 643–660.

33. KEITH, N. M.: Renal problem in disseminated lupus erythematosus, Proc. Staff. Meet. Mayo Clin., 1940, xv, 682–683.

34. Cabot Case: New Eng. Jr. Med., 1938, ccxviii, 838–843.

35. Cabot Case: New Eng. Jr. Med., 1938, ccxix, 273–277.

36. WADSWORTH, A. B.: Quoted by BAEHR ET AL.[4]

37. MAUMENEE, A. E.: Retinal lesions in lupus erythematosus, Am. Jr. Ophth., 1940, xxiii, 971–981.

38. JARCHO, S.: Lupus erythematosus associated with visceral vascular lesions, Bull. Johns Hopkins Hosp., 1936, lix, 262–273.

39. GOECKERMAN, W. H.: Lupus erythematosus as a systemic disease, Jr. Am. Med. Assoc., 1923, lxxx, 542–547.

40. REITMANN, K., and VON ZUMBUSCH, L.: Beitrag zur Pathologie des Lupus erythematosus acutus (disseminatus), Arch. f. Dermat. u. Syph., 1910, 147–180.

41. LOW, R. C., LOGAN, W. R., and RUTHERFORD, A.: A fatal case of lupus erythematosus with autopsy, Brit. Jr. Dermat., 1920, xxxii, 253–262.

42. RAVOGLI, A.: Lupus erythematosus diffusus unfortunately treated with tuberculin, Jr. Cutan. Dis., 1915, xxxiii, 266–272.

43. KEIL, H.: Relationship between lupus erythematosus and tuberculosis, Arch. Dermat. and Syph., 1933, xxviii, 765–779.

44. ROXBURGH, A. C.: Acute disseminated lupus; five fatal cases, Brit. Jr. Dermat., 1933, xlv, 95–109.

45. O'LEARY, P. A.: Prognosis and treatment of systemic lupus, Proc. Staff. Meet. Mayo Clin., 1940, xv, 686–688.

46. PELS, I. R.: Review of lupus erythematosus disseminatus, Internat. Clin., 1933, iv, 273–298.

47. APITZ, K.: Quoted by BAEHR ET AL.[4]

48. GERBER, I. E.: Quoted by BAEHR ET AL.[4]

49. PULAY, E.: Stoffwechselpathologie und Hautkrankheiten, Dermat. Wchnschr., 1921, lxxiii, 1217–1234.

50. GENNERICH, W.: Ueber die Aetiologie des Lupus Erythematodes, Arch. f. Dermat. u. Syph., 1921, cxxxv, 184–207.
51. LUDY, J. B., and CORSON, E. F.: Lupus erythematosus—increased incidence, hematoporphyrinuria and spectroscopic findings, Arch. Dermat. and Syph., 1933, xxxvii, 403–416.
52. LEWIS, T.: Quoted by KEIL.[54]
53. WILSON, J. F.: Sulfanilamide treatment of acute lupus, failure with well controlled administration, Arch. Dermat. and Syph., 1939, xl, 241–243.
54. KEIL, H.: Conception of lupus erythematosus and its morphologic variants, with particular reference to "systemic" lupus erythematosus, Arch. Dermat. and Syph., 1937, xxxvi, 729–757.
55. KEITH, N. M., and ROWNTREE, L. G.: A study of the renal complications of disseminated lupus erythematosus: report of four cases, Trans. Assoc. Am. Phys., 1922, xxxvii, 487–502.

RELATION OF EMOTIONS TO INJURY AND DISEASE: A CALL FOR FORENSIC PSYCHOSOMATIC MEDICINE *

By Hubert Winston Smith † and Stanley Cobb ‡

Cambridge, Massachusetts

I. Introduction and Historical Review

Few problems of scientific proof have been so perplexing to court and counsel, and to the expert witness, as those which arise in the "nervous shock" cases. A, intentionally or negligently, presents a psychic stimulus to B, with or without impact,§ and B alleges that in consequence he suffered "nervous shock" or some disabling injury or disease for which he should be allowed to hold A in damages. How far shall the law go in recompensing B for the alleged effects of fright or other emotions so induced, and how shall the courts deal with the problem of proof? These two questions are somewhat interrelated. We do not propose to make the instant paper a catalogue of legal cases, but to use legal doctrine as a mere background to enable us to project problems of proof and to suggest certain criteria for testing claims of causation.

Rights of recovery for invasions of personality, whether caused by direct trauma or by psychic mediation, are to be determined by the law of torts.[1] One cannot do justice to the legal doctrine of the "nervous shock" cases un-

---

§ We prefer to think of "impact" as indicating any force brought to bear on another's body or sensory apparatus, whatever the medium for transmission of the stimulus. If this concept were adopted, it would be simultaneously recognizèd that all cases of "nervous shock" involve impact, by visual, auditory or other sensory bombardment. But since the historical legal connotation of "impact" has been restricted to cases where a material object or person is brought into bodily contact with another individual, we use impact in this sense in mentioning court cases.

[1] A "tort" is a wrongful invasion of some right of personality or of property of another, causing injury in respect to which the law will give redress by money damages without proof of any contractual or consensual relations between the actor and the person acted on. Tort law might be characterized as the sum total of those legal prohibitions whereby the sphere of individual existence is protected from negligent, intended or malicious conduct of strangers. "The law of torts" is thus a generic term covering a wide variety of such wrongs, including "assault," "battery," "trespass," "conversion" (wrongful appropriation of another's personal property), "false imprisonment," "malicious prosecution" for a crime not committed, "slander and libel," "negligence," "fraud or deceit," "breach of trust," a stranger's act in "inducing breach of contract," "malpractice" of a professional man, violation of patents, trade-marks, copyrights or other vested property rights, "unfair competition" in business and other such proscribed conduct. It is through this branch of the law that such individual rights have received greatest legal protection and the citizen has been insured against unnecessary risks of injury in a crowded society.

less he keeps sharply in focus the limit of protection which the common law [2] has given to interests of personality.

(1) There is legal authority to the effect that if A, without producing any impact, *willfully* or *maliciously* causes B to suffer mental anguish, B may be allowed to recover damages without proving that any physical injury or actual disability was caused thereby.

Example: Plaintiff was a widow who supported her two minor children by the wages she earned. These wages were exempt by law from attachment and the defendant collection agency knew this fact. For the purpose of causing her mental anxiety and thus coercing her into paying a $28.75 coal bill due to one of its customers, defendant wrote a series of threatening letters. No physical violence was threatened, but plaintiff was told that a direct appeal would be made to her employer, with the assurance that this would be successful and "we will bother him until he is so disgusted with you that he will throw you out the back door." And again: "You will settle in full your account with the above through this office within the next five days or we will tie you up tighter than a drum." Defendant also intimated that plaintiff was as bad as a criminal.

Plaintiff suffered no physical injury or disability, but sued defendant for malicious invasion of mental tranquillity, alleging that the course of conduct indulged by defendant caused her mental pain, anguish and humiliation. The jury so found and returned a verdict in her favor, and from judgment entered thereon, defendant appealed to the Supreme Court of Iowa, contending that plaintiff had not proved any legal grounds for recovery of damages. That court described the legal problem presented thus: "We therefore have our problem reduced to the proposition as to whether or not recovery may be had in a case where the act is willful, as distinguished from negligent, and where there was no physical injury and no assault, and where the plaintiff in the action did not suffer from fright, but from mental pain and anguish caused by the willful act of the defendants."

Held, affirming judgment: P is entitled to recover; the willful quality of the conduct takes it out of the class of mere negligence. The Iowa Supreme Court said: "The rule seems to be well established where the act is willful or malicious, as distinguished from being merely negligent, that recovery may be had for mental pain, though no physical injury results. In such a case the door to recovery should be opened but narrowly and with due caution."

Barnett v. Collection Service, 214 Iowa 1303, 242 N.W. 25 (1932).

(Note carefully that Iowa is one of the states which refuses to permit recovery of damages for injuries due to fright without impact if the psychic stimulus is caused by the mere *negligence* of defendant. Lee v. City of Burlington, 113 Iowa 356, 85 N.W. 618 (1901).)

(2) If A, without producing any impact, *willfully* or *maliciously* does an act calculated to cause B mental anguish or nervous shock, B may recover damages for any physical injury actually caused thereby. The injury being more substantial and certain, grounds for allowing recovery here are even stronger than in (1) supra.

Example a: Plaintiff was returning home along a dark road in company with her husband when they noticed they were being pursued by another car. It had been

---

[2] The "common law" or judge-made law, consisting of the decisions and supporting opinions of the appeal courts on problems of law brought up from the trial courts, constitutes a precedent for disposing of like cases in the future, if there be no directly controlling provision of a constitution or statute.

noised about that one B, a notorious murderer, was at large in the community. In fact the pursuing car was operated by deputy sheriffs, and in their anger at plaintiff's failure to stop her machine, they fired 12 shots, one of which buried itself in the back of the front seat. Plaintiff was so prostrated by fright and nervous shock that she was confined to hospital for 13 days and to bed for six or seven weeks. She sued the deputy sheriffs and recovered a verdict and judgment from which the defendants appealed.

Held, by Michigan Supreme Court: Judgment affirmed.

Firing of the shots was an intentional act constituting an "assault" (intentionally putting another in reasonable apprehension of immediate bodily harm), and plaintiff may recover for the nervous shock even though there was no actual impact.

(Note, carefully, that Michigan is one of the states which refuses to permit recovery of damages for injuries due to fright without impact if the psychic stimulus is caused by the mere *negligence* of defendant. Nelson v. Crawford, 122 Mich. 466, 81 N.W. 335 (1899).)

Example b: Plaintiff M was a maid in the house of Y, whom a Miss X was then visiting. X claimed to have certain letters from a Major Z, among them items which Z believed to have been forged. Z desired to inspect the letters to see if they were genuine, and to that end hired defendant, D_1, a retired Scotland Yard man, now operating as a private detective, to obtain them. D_1 sent his agent D_2 to the house of X with instructions to bribe the maid if necessary. Instead, D_2 attempted to gain access to the letters by threatening M. At an interview on July 16, 1917, in X's house, D_2 told M that he was a detective inspector from Scotland Yard representing the military authorities, and that she was the woman they wanted as she had been corresponding with a German spy. In fact M was engaged to a German named Neumann, who since July, 1915, had been interned in the Isle of Man, and she had been corresponding with him against the wishes of her relatives. According to M's testimony, the threat caused her great fright and a nervous shock which expressed itself in immediate symptoms and led on to neurasthenia. There was medical testimony that such a stimulus could cause the nervous disability of which M complained, and in an action against D_1 and D_2 M got a verdict and judgment against both, for £250.

Held, on appeal, affirmed.

Janvier v. Sweeney (Court of Appeal, England), 2 King's Bench (1919) 316.

Even though the injury is not intended or desired by the actor, he nevertheless is liable in damages for actually causing it if the wrongful act which he intentionally does is one calculated to produce nervous shock. This is the rationale of Janvier v. Sweeney, supra, and of example c.

Example c: In Wilkinson v. Downton (Queen's Bench Division, Eng. 1897), 2 Q.B. 57, defendant, as a practical joke, falsely represented to plaintiff that he had been sent by her husband to say that he had been smashed up in an accident and was lying in hospital E with both legs broken, and that she was to come for him at once in a cab. The effect on plaintiff was to produce nervous shock with immediate vomiting and subsequent disability lasting for several weeks. P sued D. The appeal court upheld a verdict in P's favor for more than 100£. It stressed the fact that the stimulus was of a nature likely to upset a person of normal constitution, and took pains to say: "These consequences were not in any way the result of previous ill-health or weakness of constitution; nor was there any evidence of predisposition to nervous shock or any other idiosyncrasy."

(3) Most courts hold that if A *negligently* causes B to suffer mental anguish or transient fright, with no resulting disability or injury, B cannot

recover damages.   The law does not protect B against transient invasions of his mental tranquillity caused by mere negligence of another.

Example a: X and his wife, Y, sued D, a contractor, for negligently blasting on a railroad right of way so that stones were thrown upon the roof of plaintiff's nearby house, causing them to suffer fear and mental anxiety for the personal safety of themselves and their child.   Plaintiffs, suing on a negligence theory, recovered verdict and judgment for $264 in the trial court.

Held, on appeal: Judgment reversed: No damages can be recovered for fright, there being no other injury.

Wyman v. Leavitt (Maine Sup. Ct.), 71 Me. 227 (1880).

Example b: Defendant railway company negligently frightened plaintiff's horses, causing them to break his wagon and put him in fear of his own personal safety. Plaintiff did not allege or prove any physical injury, but obtained a jury verdict and a judgment for damages based on "great mental suffering, vexation and anxiety of mind" caused thereby.

Held, on appeal, in answer to certified questions: Judgment reversed.   There can be no recovery of damages for momentary fright or mental anguish caused by negligence of another, unaccompanied or followed by actual injury.   Gulf, Colorado and Santa Fe Railways Co. v. Trott (Tex. Sup. Ct.), 86 Tex. 412, 25 S.W. 419 (1894).

(Note that Texas is one of the states which permits recovery if *injury* or *disability* is produced by fright, negligently caused, even though there was no contemporaneous physical impact.   Gulf, etc. Railroad Co. v. Hayter, 93 Tex. 239, 54 S.W. 944 (1900).)

(4) If A negligently effects physical contact with B, the law allows B to tack on claims for mental pain and anguish caused thereby, including fright, and thus allows compensation for mental disturbance by way of what has been called "parasitic damages" when no primary recovery could be had for the latter standing alone.[8]

Example: This is well illustrated by the celebrated case of Spade v. Lynn and Boston Railroad, 168 Mass. 285, 47 N.E. 88 (1897).   Plaintiff, a hypersensitive young woman, homeward bound to Chelsea on defendant's subway train, was jostled when an inebriated strap hanger was put off the car by the conductor, and she allegedly suffered such fright from the transaction that nervous shock caused her to be ill for some time thereafter.   On the first trial no capital was made of the trivial impact with the inebriated man, and the Supreme Judicial Court treated the case as one of mere fright without impact and denied recovery for the alleged physical injury. Judgment for plaintiff was reversed and the case was remanded for a new trial.

On the second trial, plaintiff profited by this judicial lecture and alleged and proved that "The defendant conductor in removing a drunken man from the car jostled another drunken man who was standing in front of the plaintiff, and threw him upon her."   Plaintiff again recovered a verdict and judgment in the trial court. The Supreme Judicial Court treated this contact with plaintiff's body, caused by defendant, as a battery (unconsented, intended touching of another), for which the law would allow some recovery, and held that damages for "nervous shock" due to fright could be tacked on to the primary cause of action.   Justice Holmes said: "By something of an anomaly, consequences of the defendant's conduct which would not

[8] For instance, the intentional conduct may be such as to give the injured person a primary cause of action for assault, battery, trespass, malicious prosecution, defamation, wrongful arrest, seduction or some other tort.   In all these cases the courts allow the plaintiff compensation for mental anguish as a parasitic element of damages.

of themselves constitute a cause of action may at times enhance the damages, if the conduct has some other consequence for which an action lies." (Here, a battery.)

Spade v. Lynn & Boston Railroad, 172 Mass. 488, 52 N.E. 747 (1899). (Judgment reversed on other grounds.)

In the "nervous shock" cases we are confronted with a preliminary question of public policy, namely: To what extent shall the law protect interests of personality of the idiosyncratic or excessively vulnerable person against injury from stimuli created by an actor in prosecution of his legitimate affairs?

With these important points of legal principle in mind, we may turn to a historical survey of the "nervous shock" litigation to discover more about the nature of the problems that arise and the adequacy of the judicial response.

A. Recovery of damages for "nervous shock" in English law.

It is an interesting fact that no plaintiff had the audacity to make a claim in England for injury from fright or other emotional stimulus allegedly caused by negligence of another until very late in the nineteenth century. Perhaps this was due to the unwillingness of medical men, in light of then existing knowledge, to appear as expert witnesses and postulate a probable connection between stimulus and disability. However, we know from various allusions in medical literature that medical science for many centuries had entertained certain ill-defined beliefs that emotional upset of sufficient intensity might produce injurious bodily consequences. The more likely explanation for the late appearance of these cases in courts of law is that English barristers were aware that the common law of England afforded very incomplete protection against invasions of mental tranquillity. It had been settled law in England for some time that there could be no recovery for fright or other disturbance of mental tranquillity caused by mere negligence of a defendant. Indeed, this seems to be the law today not only in England but in the United States, with possibly a few unimportant exceptions.

We must remember also in connection with this problem that the concept of "nervous shock" had not crystallized to any degree during the past century, and the legal mind would naturally tend to consider nervous shock as a mere species of invasion of mental tranquillity, and so to regard it as not actionable. Which of these considerations was most responsible for late arrival of "nervous shock" cases in court must remain speculative, but the fact is that the first English case, decided in 1888, did not arise in England at all, but in Canada, and reached England on appeal to the Privy Council which then was the court of last resort for reviewing decisions of the Dominion Courts.

In Victorian Railways Commission v. Coultas,[4] the facts were that James Coultas, with his wife Mary and relatives, on May 8, 1886, at about 9:00 in

[4] (Privy Council, Eng.) 13 App. Cas. 222; 57 L. J. P. C. 69 (1888).

the evening, was driving home in a buggy, and in so doing came to a crossing over the defendant's railway line. The defendant's gate-keeper negligently opened the near gate and admitted the buggy to the crossing when it was unsafe to do so because a fast moving train was approaching. "The gate keeper directed them to go back, but James Coultas, who was driving, shouted to him to open the opposite gate, and went on. He got the buggy across the line, so that the train, which was going at a rapid speed, passed close to the back of it and did not touch it. As the train approached Mary Coultas fainted, and fell forward in her brother's arms." Thereafter an action was filed on behalf of Mary Coultas alleging that as a result of defendant's negligence in exposing her to the peril of being killed by its train, she ". . . received a severe shock and suffered personal injuries, and still suffered from delicate health and impaired memory and eye sight." The opinion of the court does not show the symptoms of which Mary Coultas complained, nor the extent or duration of her illness, but from the evidence it is safe to say that the sole diagnosis was "nervous shock." There was some medical evidence to the effect that she received a severe nervous shock from the fright and was made ill for an indeterminate time thereafter as a result. One doctor testified that he was unable to detect any physical damage, and he put down her symptoms to "nervous shock."

On this state of facts a jury in the Canadian court found that the defendant's negligence produced the injuries complained of and awarded Mary Coultas a verdict for £400. They also returned a verdict in favor of her husband in the amount of £343 2s. for medical expenses incurred in her behalf. The defendant appealed to the Supreme Court of Victoria, and on December 14, 1886, this tribunal affirmed the judgment, holding that the damages awarded were not too remote to be recovered; that proof of "impact" was not necessary; and that the female plaintiff could recover damages for physical and mental injuries caused by the fright. The defendant took a further appeal to the Privy Council (England), which reversed the judgment for plaintiffs and ordered judgment to be entered for defendant.

In arriving at this result, the English court rested its decision upon four grounds, namely:

(1) Damages of this character are too remote, because such an injury is not an ordinary consequence;

(2) To recognize a right of recover would give rise to increased litigation;

(3) The problem of proof would be very great and a wide field would be opened for fictitious suits or imaginary claims;

(4) No precedent in English law could be found from times past authorizing such a recovery.

Some of these reasons for refusing recovery are obviously vulnerable to attack. As regards the second reason assigned, it must be clear that

courts exist for the sole purpose of giving redress in proper cases, and it is no argument against recognizing a cause of action that to do so would increase litigation. Nor is the fourth reason assigned one calculated to appeal to the intelligent man. If it were true that a right of recovery could never be recognized unless some prior case on like facts had permitted recovery, the flexibility and power of growth of the common law would be lost and no means would be open for giving legal protection to entirely new species of interests or claims which arise in the progressive evolution of the social order. This, of course, has never been the law, and both the second and fourth grounds assigned by the court for refusing recovery may be dismissed as unworthy.

On the other hand, the fears which the English court felt about the problem of proof and the difficulty of sorting out the meritorious "nervous shock" cases from unmeritorious claims, was a brilliant recognition, though perhaps somewhat intuitive, that no adequate standards existed in medicine itself for appraising such claims. Furthermore, close analysis of the Coultas opinion clearly shows that the court may have been influenced in refusing recovery by a feeling that the case involved more of an invasion of mental tranquillity than any actual physical injury due to fright. It was said by one or two English writers subsequently that Mary Coultas suffered a miscarriage as a result of her fright, but it is an important and striking fact that Privy Council opinion does not mention any such physical consequence as having been caused by the stimulus. Probably we must construe the medical evidence and the language of the court together to signify that the "nervous shock," in the court's opinion, produced merely transitory symptoms with no detectable physical injury or disease. Notice, for instance, the language which Sir Richard Couch used in the opinion rendered on behalf of the Privy Council:

> "According to the evidence of the female plaintiff her fright was caused by seeing the train approaching and thinking they were going to be killed. Damages arising from mere sudden terror unaccompanied by any actual physical injury, but occasioning a nervous or mental shock, cannot under such circumstances, their Lordships think, be considered a consequence which, in the ordinary course of things, would flow from the negligence of the gate keeper. If it were held that they can, it appears to their Lordships that it would be extending the liability for negligence much beyond what that liability has hitherto been held to be. Not only in such case as the present, but in every case where an accident caused by negligence had given a person a serious nervous shock, there might be a claim for damages on account of mental injury. The difficulty which now often exists in case of alleged physical injuries of determining whether they were caused by the negligent act would be greatly increased, and a wide field opened for imaginary claims. The learned counsel for the respondents was unable to produce any decision of the English courts in which, upon such facts as were proved in this case, damages were recovered. . . . It is remarkable that no precedent has been cited of an action similar to the present having been maintained or even instituted, and their Lordships decline to establish such a precedent. They are of opinion that the first question, whether the damages are too remote, should

have been answered in the affirmative, and on that ground, without saying that impact is necessary, that the judgment should have been for the defendants."

If the court in the Coultas case meant to imply that the evidence would warrant only a finding of transient mental disturbance negligently caused by defendant, without any resulting physical injury or disability, and that this would afford no basis for recovery, the vitriolic criticism later made of this case by law writers is unwarranted, for as we have said, such in main is still the law both in England and in the United States. It must be admitted, however, that no man exists with mind so keen that he can say with certainty what the language of the Coultas case means. For purposes of 'historical analysis it is enough to say that subsequent English courts and writers, when confronted by the somewhat ambiguous language of the Coultas opinion, took it to mean that the court intended to deny a plaintiff's right to recover damages even for physical injury or disease if it occurred without impact but solely as the result of a psychic stimulus negligently created by the defendant.

The English law quickly veered in the opposite direction and recognized the right of a plaintiff to recover for physical injury caused solely from psychic stimuli to which the defendant negligently exposed him, and this even though there was no physical contact or so-called "impact." While the case of Bell v. Great Northern Railway Company [5] actually was an Irish case, its influence on English law was such that one is entitled to regard it as a starting point in the new line of reasoning. The facts of this case were quite interesting. Plaintiff, Mary Bell, a 49 year old married woman, allegedly in good health theretofore, on Sunday, June 12, 1889, took passage for an excursion on defendant's train. In the course of the journey, the train was unable to negotiate a steep incline, and the crew unhooked some of the rear coaches to allow them to roll back down the hill. Plaintiff was not on this section of the train and "the portion of the train she was in went on, and then it gave a jerk and reversed towards Armagh, and went back very fast. She heard rattling of chains and heard cries of 'Jump out; jump out: you'll all be killed.' The carriage doors were locked; and she saw people jumping out through the windows. There was a steep embankment at one side; and the train was going back very fast. Witness and all the people in the carriage were frightened. The train came to a curve, and pulled up suddenly. Witness was then standing up, and was thrown down; and the people in the carriage were all thrown about. She remembered nothing more of how she got out of the carriage; and she was in Armagh till the Monday week after the accident, and then went home to Carrickfergus."

According to plaintiff's testimony, she was unable after the accident to do anything, owing to her injuries. In a trial, the jury found that defendant was negligent in so operating the train and returned a verdict in favor of plaintiff for £300 and in favor of her husband for loss of services and medical expenses for £50.

[5] (Queen's Bench and Exchequer Div.) 26 Law Reports (Ireland) 428 (1890).

In view of the fact that this case is a cause célèbre in the law of "nervous shock," it is worth while to notice the type of evidence offered to prove injury.

"The plaintiff's daughter was examined and proved that in June, 1889, the plaintiff went on a visit to a lady in Armagh, and was up to that time in good health. The plaintiff came back about the Monday week after the accident, and witness hardly knew her; she looked as white as death, and trembled. She could not sleep at night; and when she fell asleep she awoke screaming. The plaintiff got gradually worse, and continually complained of her head and side. On the morning of July 7, 1889, at 3 o'clock, plaintiff had been in bed; and witness, who was sleeping in the next room, found her on the floor, screaming. The doctor was then called in. The plaintiff's mind was entirely deranged; and she began throwing things out of the bed. Ever since the accident plaintiff had been in bad health; previously she was the strongest woman in the house.

"On cross-examination the witness deposed that the plaintiff was very nervous, and seemed as if she had got a great fright, and been shocked. She was always talking about the train, and people jumping out, and, before the last shock, about a soldier lying dead. After July she got slightly better.

"The plaintiff's son-in-law deposed that he resided in Armagh; and hearing of the accident, drove out to the scene of its occurrence. He found the plaintiff lying on her side on the embankment, and she did not know him. He carried her to the car, and put her into it, and brought her to Armagh, where, on her arrival, she was put to bed. Witness did not believe she would live till the next morning. When the plaintiff recovered consciousness she talked very queer. She remained in Armagh till the Monday week following. Witness knew her for twenty years; and she was, up to the time of the accident, a strong, healthy woman.

"Three medical witnesses were then examined, and deposed that the plaintiff was suffering from fright and nervous shock; and one of these witnesses deposed that her condition might result in paralysis."

The defendant appealed from the judgment in favor of plaintiff. The appeal court affirmed the judgment, refusing to follow the reasoning of the Coultas case. As a matter of fact, there was enough minimal impact in the fall itself to satisfy the requirements of those modern courts which will not allow recovery for nervous shock without impact. The court made no capital of this fact, however, nor was any claim made that the physical injuries asserted to have been caused flowed in any part from the fall to the floor. The Bell case represents a complete judicial antipathy to the reasoning of the Coultas case.

The court in the Coultas case was willing to say as a matter of law that disability as a result of mere fright was too remote in expectation to be a proper element of damages. Justice Palles in the Bell case was willing to say that the proper test was whether the disability actually produced by the emotional stimulus negligently created by the defendant was a "reasonable and natural consequence of such great fright," leaving it to the jury to pass on the question. Neither court denied the possibility that a psychic stimulus might actually cause a physical result or injury, and neither court made its decision turn upon the necessity for any impact. The courts in the two

cases really differed on the score of legal policy. The court in the Coultas case felt that such injuries were too bizarre and remote in expectation to be fairly charged up against the defendant as actor, and it was reënforced by its deep doubt about the problem of proof. The court in the Bell case, it will be noted, was willing to individualize each case by leaving it to the jury to say whether the disability or injury actually caused was a reasonable and natural consequence of the fright. This point of view is probably more just and scientific than to attempt any universal generalization about remoteness of damage, such as the Coultas case indulged. On the other hand, the court in the Bell case passed over with naive complacency the difficulties of the problem of proof, being content to assume that there was not more danger of imposition in this species of case than in any other where medical testimony might be required.

It is very important to get these patterns of thought in mind, for a great many American courts have traveled the same mental paths in deciding whether they will allow recovery of damages in cases of alleged "nervous shock" without impact. The smug confidence of the court in the Bell case about the ease of protecting the purity of proof is belied by the very facts therein involved. The medical evidence of causation, as set forth in that case, is subject to serious doubt. Mrs. Bell, it will be recalled, was able to continue her journey and it was not until three weeks after the frightening stimulus that her disability appeared, an interval too long to warrant the drawing of a causal connection between stimulus and effect. Furthermore, the case indicates that she suffered from symptoms suggestive of a preëxisting neurological or psychiatric disorder. There are allusions in the record to "before the last shock," and the like, showing that distinct shocks were suffered some time after the fright stimulus was generated and indicating that Mrs. Bell's complaints probably arose from independent cerebral vascular accidents not connected in any way with her frightening experience. It is interesting and somewhat anomalous that in the Bell decision, which is thought to have laid down a just basis for recovery in the nervous shock cases, the verdict itself in favor of plaintiff was probably unjust.

This result arises from the fact that courts of law were not then able to weigh the sufficiency of medical evidence, a situation which is largely true even today. As a crude response to this problem, the courts early adopted the view that medical testimony was to be treated like ordinary lay testimony, and if there were substantial disagreement between witnesses, the jury should be entitled to credit either version. This means that if two doctors appear in court, knowing nothing about the mechanisms of nervous shock, but willing to assert opposite conclusions in the form of expert opinions, there is no means whatever for preventing a miscarriage of justice except the hopeful but remote possibility that the lay jury in guessing might in some cases hit upon the right answer.

By a succession of cases the doctrine of the Bell case has been uniformly upheld in England both in ordinary tort actions and in workmen's compensa-

tion proceedings. In England a plaintiff may recover for actual injury or disability caused by a psychic stimulus negligently presented by a defendant actor, without any need for demonstrating so-called "impact." [6]

B. American decisions on nervous shock.

The first American cases began to come into court almost contemporaneously with the early Irish and English cases. American judges had to deal with the same plexus of problems and policy considerations which confronted the English courts. They either reacted sympathetically to the Coultas view or reached an opposite result, following the line of English cases ushered in by the Bell decision. Whatever the formulations and reasons pressed into service in recognizing or refusing a right of action for "injury without impact," one of the salient factors has been the judicial attitude toward difficulties of proof.

Many American courts have felt that a bar cannot be set up against all meritorious claims simply because imposition or fraud may sometimes creep in and shabby claims get unmerited redress. They feel that the balance of injustice is less if the court recognizes a right of action and assumes the risks inherent in the problems of proof.[7]

[6] Actually, the first case of nervous shock without impact was the unreported Irish case of Byrne v. Great Southern and Western Railway Company (1882) in which plaintiff, a telegraph operator in defendant's station, got a severe fright when a negligently set switch permitted D's locomotive to enter a siding, break down a permanent buffer and destroy one wall of the telegraph office. We have no record of the medical testimony, but plaintiff apparently suffered more than temporary disability from the fright, for he was awarded damages of 325£. On cross-examination, the plaintiff said: "A hair of my head was not touched; I swear I received no physical injury; I got a great fright and shock; I do not mean a physical shake; it was the crash and falling in of the office, and shouts of the clerks saying they were killed; I saw part of the office falling in; I believed it was all falling in."

The Court in the Coultas case evidently was unaware of this legal precedent, but Justice Palles, in the Bell case, called attention to it and mentioned the fact that he personally was the trial judge who presided over the Byrne case.

Subsequent English authorities have followed the Bell case: Dulieu v. White & Sons, 17 The Times L.R. 555, 2 K.B. 669 (1901); Hambrook v. Stokes Brothers, Ltd., 41 The Times L.R. 125 1 K.B. 141 (1925).

The Scottish courts have consistently allowed recovery for disability due to nervous shock, negligently caused, without requiring any impact. Cooper v. Caledonian Ry., (1902) 4 F. 880, Ct. of Sess.; Gilligan v. Robb, (1910) S.C. 856, Ct. of Sess.; Coyle v. Watson, (1915) A.C. 1; Brown v. Glasgow Corp., (1922) S.C. 527, Ct. of Sess.; Currie v. Wardrop, (1927) Scottish Law Times 383.

[7] Courts of the following American states allow recovery for injury or disability due to psychic stimuli, negligently caused by defendant, without necessity for proving physical impact:

Ala. Alabama Fuel & Iron Co. v. Baladoni, 15 Ala. App. 316, 73 So. 205 (1916).
Cal. Lindley v. Knowlton, 179 Cal. 298, 176 Pac. 440 (1918).
Ga. Goddard v. Watters, 14 Ga. App. 722, 82 S.E. 304 (1914).
Ia. Watson v. Dilts, 116 Iowa 249, 89 N.W. 1068 (1902).
Kan. Whitsell v. Watts, 98 Kan. 508, 159 Pac. 401 (1916).
La. Stewart v. Arkansas Southern R. Co., 112 La. 764, 36 So. 676 (1904).
Md. Green v. Shoemaker, 111 Md. 69, 73 Atl. 688 (1909).
Minn. Purcell v. St. Paul City R. Co., 48 Minn. 34, 50 N.W. 1034 (1892).
Neb. Hanford v. Omaha Street R. Co., 113 Neb. 423, 203 N.W. 643 (1925).
N. H. Chinchiolo v. New England Wholesale Tailors, 84 N. H. 329, 150 Atl. 540 (1930).
N. C. Kimberly v. Howland, 143 N. C. 398, 55 S.E. 778 (1906).
Ore. Salmi v. Columbia, etc. R. Co., 75 Ore. 200, 146 Pac. 819 (1915).
R. I. Simone v. Rhode Island Co., 28 R. I. 186, 66 Atl. 202 (1907).
S. C. Mack v. South-Bound R. Co., 52 S. C. 323, 29 S.E. 905 (1897).

Other courts, of which Massachusetts, New York and Pennsylvania are noteworthy examples, have felt that some further guarantee is necessary. This is satisfied if contemporaneously with the emotional stimulus, such as fright, the defendant by his negligence also causes an impact against the plaintiff's body. This was an attractive and plausible device, to the legal mind, for letting down the bars against recovery of damages. In the first place, as we have seen, the negligent impact itself would give the plaintiff an independent cause of action for at least some damages, and this enabled the courts to make use of the historical custom of tacking on "parasitic damages" as a means of compensating consequences of "nervous shock." Secondly, it was felt that the defendant as actor was here more culpable in terms of fault. Thirdly, some guarantee against simulation or fraud would exist, if the plaintiff had to prove actual impact, as this would tend to verify the fact that plaintiff was actually present at the scene of the accident and within the range of defendant's stimulus. Fourthly, in the first promulgation of this doctrine, there was doubtless a bona fide supposition that the impact would be severe enough so that one could not say what part of the "nervous shock" was due to the blow and what part was due to the psychic stimulus. It was easy to reason that the law need not be tender with the wrong-doer, and an exact scientific method of proof would not be insisted upon. This is what we may well characterize as the purely pragmatic approach early adopted by the Massachusetts courts. The essential position of these jurisdictions is that no analytical ground in tort law can be found for a blanket refusal of liability in cases of "injury without impact," but that practical considerations of policy and proof make it necessary to refuse recovery unless plaintiff can prove some contemporaneous impact.[8]

Presence or absence of impact can have no justifiable relation to the matter unless the courts further require that the physical impact be of such character that it can produce a substantial part of the nervous shock. In

S. D. Sternhagen v. Kozel, 40 S. D. 396, 167 N.W. 398 (1918).
Tenn. Memphis St. R. Co. v. Bernstein, 137 Tenn. 627, 194 S.W. 902 (1917).
Tex. Gulf, etc. R. Co. v. Hayter, 93 Tex. 239, 54 S.W. 944 (1900).
Wash. O'Meara v. Russell, 90 Wash. 557, 156 Pac. 550 (1916).
Wis. Pankopf v. Hinkley, 141 Wis. 146, 123 N.W. 625 (1909).

[8] Courts of the following American states deny recovery for injury due to fright or other psychic stimuli, negligently caused by defendant, if there is no contemporaneous physical impact:

U. S. Haile's Curator v. Texas & Pacific R. Co. (U. S. Cir. Ct. of App., Fifth Cir.), 60 Fed. 557 (1894). (Federal courts now must follow the tort law of the state in which they are situated.)
Ark. St. Louis, etc. R. Co. v. Bragg, 69 Ark. 402, 64 S.W. 226 (1901).
Ill. Braun v. Craven, 175 Ill. 401, 51 N.E. 657 (1898).
Ind. Terre Haute Electric R. Co. v. Lauer, 21 Ind. App. 466, 52 N.E. 703 (1899).
Ky. McGee v. Vanover, 148 Ky. 737, 147 S.W. 742 (1912).
Mass. Spade v. Lynn, etc. R. Co., 168 Mass. 285, 47 N.E. 88 (1897).
Mich. Nelson v. Crawford, 122 Mich. 466, 81 N.W. 335 (1899).
Mo. McArdle v. Peck Dry Goods Co., 191 Mo. App. 263, 177 S.W. 1095 (1915).
N. J. Ward v. West Jersey, etc. R. Co., 65 N. J. L. 383, 47 Atl. 561 (1900).
N. Y. Mitchell v. Rochester Ry. Co., 151 N. Y. 107, 45 N.E. 354 (1896).
O. Miller v. Baltimore, etc. R. Co., 78 Oh. St. 309, 85 N.E. 499 (1908).
Pa. Ewing v. Pittsburgh, etc. R. Co., 147 Pa. St. 40, 23 Atl. 340 (1892).

practice, those courts which started out bravely to espouse the position that there can be no recovery for 'injury without impact' because of the likely promotion of fraud, have themselves prostituted their ideal. Inspection of the cases in the various jurisdictions shows that today the most trivial impact is held adequate to enable a recovery. For instance, the Massachusetts courts first held that a superficial bruise was enough,[9] and later went to the extreme of holding that a mere impact without visible discoloration would suffice, for one could not say that the impact did not cause internal injury.[10]

This tendency to make of "impact" a mere nominal prerequisite to a right of action for nervous shock is seen in the decisions of practically all the courts which follow the minority view. In the recent New York case of Comstock v. Wilson,[11] plaintiff was riding with her husband when the defendant negligently struck the back of their car with his own machine. The collision was a minor one, but it produced some noise or "grating sound" without inflicting any personal injury. One could not very well predicate more than a slight impact due to jarring of decedent as she sat in her husband's car. She promptly stepped from the car and started to write down the defendant's name and license number, all within a few minutes of the accident. While so doing she fainted and fell to the sidewalk, fracturing her skull and died within 20 minutes of that time. Decedent's husband brought an action for damages against defendant and recovered a verdict in the trial court for $5,000. On appeal this was affirmed. The court held that the slight jarring of decedent was sufficient to satisfy the requirement of an "impact."

Obviously, the test of "impact" has become a mere formal requisite, and on that ground the minority courts have been severely criticized for not dispensing with it altogether. As things now stand, plaintiffs in the minority

[9] Driscoll v. Gaffey, 207 Mass. 102, 92 N.E. 1010 (1910). (Defendant's negligent blasting caused a 20 pound stone to be thrown on P's house with a loud noise; P was frightened and fell to the floor receiving only a superficial bruise. Held: This impact was injurious enough to permit recovery for neurasthenia attributed by doctors to contemporaneous fright.)

[10] Kisiel v. Holyoke Street Railway Co., 240 Mass. 29, 132 N.E. 622 (1921). (Plaintiff, a pregnant woman, while a passenger on D's street car, was slightly jarred by a negligent rear end collision with another of D's cars, and she alleged that fright caused an abortion. Held, affirming judgment for plaintiff entered on jury verdict: The impact was sufficient; though the bump may have produced no outwardly visible physical injury, it may have produced internal injury.) Note, that in Freedman v. Eastern Mass. Street Ry. Co., 299 Mass. 246, 12 N.E. (2d) 739 (1938), the Supreme Judicial Court of Massachusetts definitely makes the requirement for recovery, "physical injury from without" as contrasted with injury due to "the purely internal operation of fright." Plaintiff, a passenger on D's street car, was so frightened by a negligent side to side collision with a truck that she jumped from her seat and in so doing twisted her shoulder. The trial court directed a verdict for defendant because there was no proof of an impact. Held: Such proof is not necessary where, as here, defendant's negligence causes physical injury from without.

Comment: At first this distinction may seem tenuous, but it is substantial in terms of making proof. Most other courts have held that if A creates in B a reasonable apprehension of bodily peril, and B injures himself in trying to escape the danger, he can hold B in damages, even though fear was a link in the chain of causation. The injury is physical (broken leg, etc.) and immediate, and there is no such difficulty with conjectural causation as one finds in the usual nervous shock cases.

[11] 257 N.Y. 231, 177 N.E. 431 (1931).

jurisdictions have every inducement to claim some fanciful or fraudulent impact in order to gain a right to recover for "nervous shock." The frauds which the court hoped to hold out by closing the door have crept in through the open window.

As a matter of fact, there was a great deal of practical force and merit in the original refusal of the Coultas case (Eng.) and of the Spade and Homans cases (Mass.) to allow recovery in the "nervous shock" cases on the supposition that more frauds would be encouraged by an opposite rule than meritorious cases cut off. The systematic study of the relations of emotions to injury and disease did not begin until about 1929 when Cannon [15] published his book. Previously many assertions made in court regarding disease or injury caused by fright or other psychic stimuli involved more supposition and conjecture than systematized knowledge or experience of the medical profession. Our impression from considering a great number of the legal decisions is that the "impact" requirement as a guarantee of merit has utterly failed in its purpose of filtering out valid claims for "nervous shock" from shabby ones. The attempt of the courts to press into service such a simple sifting device was fore-doomed to failure, for it had no scientific basis. Probably it is true that until recently the balance of justice and equity would have been served by refusing recovery in ordinary cases of "nervous shock" in accordance with the premonition of the Coultas case.

Inspection of the decided cases shows a hopeless lack of any scientific criteria in assessing the merit of particular claims. It is interesting to find that the appeal courts are completely unable at present to appraise the sufficiency of proof of causation. The result is that any doctor who is willing to do so can put forward a categorical opinion to the effect that causation of the alleged injury has medical support, and thus make a case for the jury, when the opinion represents sheer personal speculation and conjecture.

We hasten to add, however, that we are now gaining the medical knowledge necessary to enable a fair appraisal of these claims. Psychosomatic medicine is bringing together with beneficial convergence this whole series of problems regarding what injuries or diseases may be caused by emotional stimuli. Though until recently the balance of arguments was with the Coultas view denying liability (despite adverse criticism of law writers), the augmentation of scientific knowledge has altered the situation. All courts should now recognize a right of action for "injury without impact," on the ground that the old practical arguments against allowing a right of action have lost their force, since we are in position to supply scientific criteria of validity heretofore not available. The minority jurisdictions should shift their view in keeping with this new scientific accession of knowledge. They may do this either by renouncing past decisions, or by taking up a new definition of "impact" as suggested in our initial footnote, recognizing that "nervous shock" always involves impact although the sensory bombardment may be through sound, light or heat waves. A more valuable guarantee of actual causation of the injury by the stimulus would be to insist upon im-

mediate appearance of the harm or of satisfactory "bridging" symptoms to fill the interval between stimulus and alleged response.

It is the purpose of this paper to put forward a rationale of "nervous shock" and its possible consequences which may have some value as criteria of scientific proof, both for the expert witness and for courts.

II. Consideration of "Nervous Shock" and of Injuries and Diseases Which May Result Therefrom

We find from reviewing the law cases that the most numerous claims for injury or disease caused by psychic stimuli fall into these groups:

(1) Miscarriage or abortion.[12]

(2) "Traumatic neuroses." This condition is included because in a majority of cases the impact is not a substantial cause of the neurosis but only an occasion for the expression of symptoms.[13]

(3) "Nervous shock," allegedly resulting in disability, injury or disease. In our discussion we exclude all those cases where there has been a mere transient disturbance of emotional or mental tranquillity, rapidly disappearing without resultant disability. It is not surprising to find that the important psychic stimulant which the plaintiff seeks to incriminate in the majority of these cases is fright, for that is the emotion most likely to be engendered by realization of sudden peril or danger. Usually the defendant has negligently brought a railway locomotive or some other dangerous force into close proximity with plaintiff, so as to threaten some immediate bodily harm, and this gives rise to the plaintiff's emotional response.

Since we propose to leave the first two categories of claims to others for discussion, it seems appropriate that we give a clinical characterization of "nervous shock" and the mechanism of its action, before proceeding to suggest a definite legal rationale for disposing of individual cases.

Definitions

Emotional states are difficult to define, because they have both a subjective and objective aspect.[14] They are complex reactions in the human animal, reactions that arise in response to environmental stimulation or the memory thereof. The subjective part is an acute awareness of various bodily sensations and diffuse feelings not easily referable to any organ; the aroused awareness itself is an important part of the picture. The objective part of emotion is that which is seen when one observes critically a person suffering emotional stress, e.g., the muscular tension, motor restlessness, tremor, expressive intonation of voice, wide pupils, sweating, pallor of face, cold hands and all the other autonomic reactions described by Cannon as preparation

---

[12] These cases are very numerous and criteria of proof are needed for both traumatic and psychic abortion. Because the subject, in its details, calls for special treatment, we exclude it from the present study. See Hertig and Sheldon, Minimum criteria required to prove prima facie case of traumatic abortion or miscarriage, *in* Smith on Scientific Proof and Relations of Law and Medicine, Albany, N. Y., Matthew Bender & Co., (In press).

[13] See Smith, H. W., and Solomon, H. C.: Traumatic neuroses in court, *in* Smith on Scientific Proof and Relations of Law and Medicine, *id.*

[14] Bridges, J. W.: Outline of abnormal psychology, 1931, R. G. Adams & Co., Columbus.

for emergency. Emotions are commonly classified as Fear, Rage, Grief, Loneliness and Love, with many subdivisions. The old theory of James and Lange, that emotions (the subjective part) are the result of the visceral changes (objective part), is no longer tenable. Cannon [15] has demonstrated that animals can show signs of emotion when the viscera are separated from the brain by cutting the autonomic nerves.

Injury is used in this paper as meaning harmful changes in the organism caused by environmental forces of a mechanical nature. The evidence for these changes may be either the detection of abnormal functions or the seeing of lesions. A lesion is defined as visible abnormality of tissue in contrast to submicroscopical and chemical changes in structure. The naive dichotomy "organic vs. functional" is denied.

Disease is the process which causes all harmful changes in the organism other then those caused by injury.

Psychosomatic medicine includes, strictly speaking, any branch of medicine where both psychology and physiology are concerned. The body or "soma" is the whole of the organism except the reproductive cells. The *"psyche"* is the result of function of the more highly integrated parts of the central nervous system; the functions that are commonly considered "psychological." [16] Since all organs are more or less controlled by the nerves that run to them from the central nervous system, and since psychological functions might effect such control, all medicine might be considered "psychosomatic." From a practical standpoint, however, one must consider "psychosomatics" as of 1943; just now it is a field of clinical medicine that is attracting much attention because new knowledge in psychology and in clinical medicine indicates the psychogenesis of many symptoms (abnormalities of function) and even of some lesions. In short "psychosomatic medicine" is the clinical field where the internist or medical specialist can help the psychiatrist, and where the psychiatrist can help the medical man in the study and treatment of disease.

The Evidence That Emotions May Cause Disorders of Function. Observations on the effect of the emotions upon the bodily functions are as old as medical science and as varied as the combinations of personalities and situations would mathematically suggest. Nevertheless, certain combinations have occurred over and over again, and these have become recognized clinical "facts." The evidence is convincing to most medical men that there is a cause and effect relation between the emotional stress and the symptoms, but the phenomena are striking only because of common occurrence. The "proof" that they are causally connected is only of the *"post hoc ergo propter hoc"* variety; no physiological mechanisms, no series of pathological processes are known to explain the symptoms. There is so much of this clinical observation that it cannot all be discussed in a single paper; it fills volumes in the literature. Three recent books probably summarize it satisfactorily. The most recent and thorough is Dunbar's "Emotions and Bodily Changes." [17] Here one may find a great number of clinical examples abstracted from 2251 different contributions. Much of it is only expression of opinion, but there is a great deal of good observation that cannot be ignored. In 1930 Leopold Alkan published an important book "Ana-

[15] CANNON, W. B.: Bodily changes in pain, hunger, fear and rage, 1929, Appleton & Co., New York.

[16] COBB, S.: Borderlands of psychiatry, 1943, Harvard University Press, Cambridge, Mass.

[17] DUNBAR, H. F.: Emotions and bodily changes, 1935, Columbia University Press, New York.

tomische Organkrankheiten aus seelischer Ursache" [18] in which he shows how motor disturbances of hollow organs and tubular organs can lead to spasms with resulting stasis, infection and necrosis. He also shows how secretions of glands may be affected by nervous stimulation to cause symptoms. This book is based on clinical observations. It is interesting reading but the author seems a little too ready to accept an interesting combination of circumstances as proof for a theory.

The third book is Fritz Mohr's "Psychophysische Behandlungsmethoden," [19] which gives evidence of a different kind. He tells of 20 years' experience in "curing" people, i.e., removing symptoms by psychological methods. It is a good contribution, although evidence of this sort can often be interpreted in more than one way.

Modern "Psychosomatics" may be said to have really begun with Walter B. Cannon, when he published his book "Bodily Changes in Hunger, Fear, Pain and Rage." [15] Pavlov and others had given physiological evidence of such mechanisms, but Cannon brought the subject to an issue and formulated a theory which has profoundly affected the thinking of physicians and psychiatrists throughout the world. In his second great book "The Wisdom of the Body" [20] Cannon sums up the responses of an animal to powerful emotion as follows:

It is remarkable that most of these reactions occur as the accompaniment of the powerful emotions of rage and fear. Respiration deepens, the heart beats more rapidly, the arterial pressure rises, the blood is shifted away from the stomach and intestines to the heart and central nervous system and the muscles, the processes in the alimentary canal cease, sugar is freed from the reserves in the liver, the spleen contracts and discharges its content of concentrated corpuscles, and adrenin is secreted from the adrenal medulla.

The emotional responses just listed may reasonably be regarded as preparatory for struggle. They are adjustments which, so far as possible, put the organism in readiness for meeting the demands which will be made upon it. The secreted adrenin cooperates with sympathetic nerve impulses in calling forth stored glycogen from the liver, thus flooding the blood with sugar for the use of laboring muscles; it helps in distributing the blood in abundance to the heart, the brain, and the limbs (i.e., to the parts essential for intense physical effort) while taking it away from the inhibited organs in the abdomen; it quickly abolishes the effects of muscular fatigue so that the organism which can muster adrenin in the blood can restore to its tired muscles the same readiness to act which they had when fresh; and it renders the blood more rapidly coagulable. The increased respiration, the redistributed blood running at high pressure, and the more numerous red corpuscles set free from the spleen provide for essential oxygen and for riddance of acid waste, and make a setting for instantaneous and supreme action. In short, all these changes are directly serviceable in rendering the organism more effective in the violent display of energy which fear or rage may involve.

Taking the systems and organs mentioned by Cannon as responding physiologically to fear and rage, one can make a table showing the disorders of

[18] ALKAN, L.: Anatomische Organkrankheiten aus seelischer Ursache, 1930, Hippokrates, Stuttgart.

[19] MOHR, F.: Psycho-physische Behandlungsmethoden, 1925, Hirzel, Leipzig.

[20] CANNON, W. B.: Wisdom of the body, 1932, Norton, New York.

these systems best known to accompany emotional stress in man.   We do not assert that the emotional stress is the primary or sole cause of these disorders, though in some instances this may be true, but rather that emotions may excite an attack or aggravate one already in progress.   Only those disorders are listed for which there is abundant clinical evidence.

TABLE OF CLINICAL DISORDERS PROBABLY RELATED TO EMOTIONAL STIMULATION

Arranged by systems and followed by a good reference which has adequate bibliography. Emotions may be related to the diseases listed as (1) exciting causes of an attack or (2) aggravating factors after an attack is started.   Both would apply to all the diseases.   A single powerful stimulus has been known to produce an attack in those marked (S) although usually a long bombardment with emotional stimuli is needed.

Respiratory System
    Bronchial asthma (S)   French and Alexander [21]
    Hyperventilation tetany (S)   Talbott, Cobb, et al [22]
    DaCosta's syndrome (S)   Wood [23]
Cardiovascular System
    Angina pectoris (S)   Fahrenkamp [24]
    Hypertension (S)   Weiss [25]
    Neurocirculatory asthenia (S)   Wood [23]
Muscular and Skeletal Systems
    Rheumatoid arthritis   Cobb, Bauer, Whiting [26]
    Tremors and contractures (S)   Babinski and Froment [27]
Alimentary (Gastrointestinal) System
    Mucous colitis (S)   White, Cobb, Jones [28]
    Peptic ulcer   Wolf, Wolff [29]
    Dyspepsia and "gastritis" (S)   Mittelmann and Wolff [30]
Genitourinary System
    Retention of urine (S)   Schwarz [31]
    Enuresis (S)   Michaels [32]
    Impotence (S)   Schwarz [31]
    Dysmenorrhea (S)   Novak, Harrik [33]
Endocrine System
    Thyrotoxicosis (Basedow or Graves' Disease) (S)   Mittelmann [34]
    Diabetes Mellitus   Liebig [35]
Anorexia Nervosa   Richardson [36]
Integument (skin)
    Neurodermatitis (S)   Greenhill, Finesinger [37]
    Psoriasis   Bunnemann [38]

[21] FRENCH, T. M., and ALEXANDER, F.: Psychogenic factors in bronchial asthma, Psychosom. Med. Monogr., 1941, II and IV.

[22] TALBOTT, J. H., COBB, S., COOMBS, F. S., COHEN, M. E., and CONSOLAZIO, W. W.: Acid-base balance of the blood in a patient with hysterical hyperventilation, Arch. Neurol. and Psychiat., 1938, xxxviii, 973.

[23] WOOD, P.: DaCosta's syndrome (or effort syndrome), Brit. Med. Jr., 1941, i, 767, 805, 845.

[24] FAHRENKAMP, K.: Der Herzkranke, 1931, Hippokrates, Stuttgart.

[25] WEISS, E.: Cardiovascular lesions of probable origin in arterial hypertension, Psychosom. Med., 1940, ii, 249.

[26] COBB, S., BAUER, W., and WHITING, I.: Environmental factors in rheumatoid arthritis, Jr. Am. Med. Assoc., 1939, cxiii, 668.

[27] BABINSKI, J., and FROMENT, J.: Hysteria or pithiatism, 1918, University of London, London.

[28] WHITE, B. V., COBB, S., and JONES, C. M.: Mucous colitis, Psychosom. Med. Monogr., 1939, I.

[29] WOLF, S., and WOLFF, H. G.: Genesis of peptic ulcer in man, Jr. Am. Med. Assoc., 1942, cxx, 670.

[30] MITTELMANN, B., and WOLFF, H. G.: Emotions and gastroduodenal function; experimental studies on patients with gastritis, duodenitis and peptic ulcer, Psychosom. Med., 1942, iv, 5.

The nervous system is not included in the table because it functions largely as an intermediary mechanism for the conduction of nerve impulses from sense organ or to muscles and glands. The nervous system, especially the autonomic nervous system, acts as a pathway, not as an organ system. It is the behavior of those muscles and glands that make the symptoms discussed under each of the headings above. The muscles involved are mostly the smooth muscles of blood vessels and viscera, but the skeletal muscles may be involved. The psychological phenomena stimulated by emotions can hardly be called psychosomatic; they are psychiatric problems.

The proposition that the symptoms found in the various disorders listed are mostly the result of hyperfunction of the autonomic nervous system can be illustrated by many clinical observations. For example, fear or anger when excessive causes pallor and relaxation of the stomach, whereas anxiety and recurrent annoyances cause hypermotility, hyperemia and hypersecretion. Spasm of blood vessels causes people to become "pale-with-emotion" in the face, hands and stomach. Different degrees of emotion or different personal reactions can cause flushing of the face, neck and rectum.[39] Vomiting and urgent urination are common accompaniments of fear. Thus, Cannon's concept of sympathetic stimulation as a reaction to fear and preparation for flight or fight, is a useful basis for the understanding of many, if not most psychosomatic disorders. The endocrine glands and the autonomic nervous system are the great mediators between psyche and soma. Through them emotions are *expressed* (sic) as normal actions or symptoms.

Of course it is arbitrary to make a distinction between a disorder of function and a disorder of structure. It is a naïve idea arising from the good old days when only "seeing was believing." Unfortunately it has led to a common but harmful clinical slang which divides all disease into "functional" or "organic." In this slang "functional" is not used in the physiological sense (or it would include all symptoms) and "organic" is loosely thought to mean a "structural" change or "lesion." Any scientist should know nowadays that a chemical change is just as "structural" as a lesion

[31] SCHWARTZ, O.: Psychogenese und Psychotherapie körperlicher Symptome, 1925, Springer, Berlin.

[32] MICHAELS, J. J., and GOODMAN, S. E.: Enuresis and other factors in normal and in psychotic persons; comparative study of incidence and intercorrelations, Arch. Neurol. and Psychiat., 1938, xl, 699.

[33] NOVAK, J., and HARNIK, M.: Die psychogene Entstehung der Menstrualkolik und deren Behandlung, Ztschr. f. Geburtsh. u. Gynäk., 1929, xcvi, 239.

[34] MITTELMANN, B.: Psychogenic factors and psychotherapy in hyperthyreosis and rapid heart imbalance, Jr. Nerv. and Ment. Dis., 1933, lxxvii, 465.

[35] LIEBIG, H.: Trauma und Diabetes mellitus, Med. Klin., 1932, xxviii, 357.

[36] RAHMAN, L., RICHARDSON, H. B., and RIPLEY, H. S.: Anorexia nervosa with psychiatric observations, Psychosomat. Med., 1939, i, 335.

[37] GREENHILL, M. H., and FINESINGER, J. E.: Neurotic symptoms and emotional factors in atopic dermatitis, Arch. Dermat. and Syph., 1942, xlvi, 187.

[38] BUNNEMANN, O.: Neue Beiträge zur Frage der Psychogenese von Hautsymptomen, Ztschr. f. d. ges. Neurol. u. Psychiat., 1924, lxxxviii, 589.

[39] WHITE, B. V., and JONES, C. M.: Effect of irritants and drugs affecting the autonomic nervous system upon the mucosa of the normal rectum and rectosigmoid with especial reference to "mucous colitis," New England Jr. Med., 1938, ccxviii, 791.

caused with an axe. There can be no line between structure and function, between an organ at rest and an organ in action. For convenience and to avoid the stultifying conception of the dichotomies "organic or functional," "physical or mental" diseases should be considered as arising from at least four sources: hereditary (genogenic), chemical (chemogenic), visible tissue damage (histogenic) and psychological disorders (psychogenic).[40]

The Evidence That Lesions May Be Caused by Emotional Trauma. (a) Psychogenic lesions appearing in apparently healthy persons. The basic observation that leads on to all other considerations of psychogenic lesions is that a blister can be raised on the skin by hypnotic suggestion and removed by the same means. Three competent observers with expert witnesses have reported that this can happen—Kreibrik (1907), Kohnstmann and Pinner (1908), and Schindler (1927). The latter wrote a monograph in which he describes not only blisters, but subcutaneous hemorrhages caused by hypnosis and eliminated by hypnosis.[41] Dunbar[17] reviews the literature and gives several other references.

The reason this is spoken of as the basic observation is because it is direct, with no complicating steps that need explanation. If it is accepted as a fact many psychogenic phenomena become credible, and the great variety of clinical phenomena (listed above) have a plausible origin in emotional stress.

A more complicated series of events, but one that is now well proved by the work of Wolff[29] is that leading to peptic ulcer. His preliminary studies on gastric motility and reaction in relation to emotional stimuli[30] gave presumptive evidence that peptic ulcer could arise from nervous tension. His recent remarkable studies on a man with a gastrostomy seem to prove the relationship. The mucosa of this man's stomach could be seen through the artificial mouth. When he was anxious and resentful, there was increased acid secretion, the mucosa became hyperemic and motility increased. If these changes were severe and continued, small hemorrhages appeared beneath the mucous membrane, causing erosion of the surface. In a few instances when the acid hypersecretion was not kept away from the surface of the mucous membrane by the protective layer of mucous, a chronic ulcer developed. In Wolff's[29] words: "it appears likely, then, that the chain of events which begins with anxiety and conflict and their associated overactivity of the stomach and ends with hemorrhage or perforation is that which is involved in the natural history of peptic ulcer in human beings."

In cardiospasm[18] a somewhat similar mechanism is seen. At the cardiac end of the stomach, just below the esophagus a spasm of muscle may take place when the patient is emotionally upset. This closes the entrance to the stomach, saliva, mucous and food collect in the esophagus, vomiting occurs, and the lower part of the esophagus is dilated and often shows erosions and infection of the mucous membrane. In chronic cases these lesions (fusiform dilatation, mucosal erosion) are seen at autopsy but the ring of muscle

[40] COBB, S.: Foundations of neuropsychiatry, 1941, Williams and Wilkins, Baltimore.
[41] SCHINDLER, R.: Nervensystem und spontane Blutungen, 1927, Karger, Berlin.

at the cardia, that caused them by its obstructive spasm, has relaxed in death and appears normal.

A quite different sort of lesion is found in cases of hysterical paralysis of long duration.[27] The unused muscles become atrophied and fibrotic holding the limb almost immobile by the muscular contractures. These muscular lesions, however, can be considered a secondary result through disuse; some direct trophic change in the muscle, however, is a possibility.

(b) Psychogenic lesions appearing in patients with an hereditary predisposition. Persons who appear healthy and normal may yet be unusually susceptible to emotional shock because of an inherited instability of certain organ-systems. Perhaps the best example is what Means [42] describes as the patient who is like a "loaded gun"; she has inherited a tendency to thyrotoxicosis, and when a severe emotional trauma comes into her life, it, so to speak, "pulls the trigger" and the full blown syndrome of Graves' disease can appear in 48 hours, with exophthalmos, enlarged thyroid and increased metabolic rate; later hypertrophy of the thyroid may develop and myocardial damage. There are so many cases cited that only two references will be given to especially striking reports.[43, 44]

Raynaud's disease is another good example of psychogenic lesions appearing in a susceptible person. In these patients there is probably an inherited tendency to spasm in the small vessels of the hands and feet causing cold and white extremities. In marked cases these vascular spasms lead to such prolonged asphyxia of the tissues that necrosis results, with ulceration appearing on the fingers or toes. The onset of the spasms of the small vessels has been observed under the microscope, and seen to occur in definite relationship to emotional stimulation.[45, 46] White hands or fingers often occur in these patients immediately after emotional stress, and if the situation is prolonged the ulcerations appear.[47]

(c) Psychogenic increase of lesions already present. The killing of patients with angina pectoris by emotional excitement is an everyday occurrence. It is said that every radio broadcast of a prize-fight has several "cardiac" victims. In these cases the blood supply to the heart is already decreased by disease of the coronary arteries and a spasm of these vessels set up by emotional stimulation may cause an infarct of the heart muscle with focal necrosis and stoppage of the heart.[48]

[42] MEANS, J. H.: Thyroid and its diseases, 1937, Lippincott Co., Philadelphia.

[43] RAHM, H.: Zur Pathogenese und Therapie des Morbus Basedow, Nervenarzt, 1930, iii, 1.

[44] ROUSSY, G., and CORNIL, L.: La maladie de Basedow et la guerre, Presse méd., 1920, xxviii, 753.

[45] FREMONT-SMITH, F.: Personal communication.

[46] DEUTSCH, F.: Capillary studies in Raynaud's disease, Jr. Lab. and Clin. Med., 1941, xxvi, 1729.

[47] COBB, S.: Borderlands of psychiatry, case No. 1, Ch. I, 1943, Harvard Univ. Press, Cambridge, Mass.

[48] WHITE, P. D.: Scientific Proof in Respect to Injuries of the Heart, in Smith on Scientific Proof and Relations of Law and Medicine, Matthew Bender & Co., Albany, N. Y., in press.

Several other types of immediate death due to emotional shock or psychological disorder have been described, but in none except angina pectoris is the mechanism simple and direct enough to constitute proof.

III. Rationale for the "Nervous Shock" Cases

In developing a rationale for the nervous shock cases, it is not possible to divorce scientific considerations from legal theory. It is useful, in arriving at the legal components of this problem, to bear constantly in mind the essential ingredients of any cause of action.

A plaintiff who seeks to recover money damages in a court of law has the burden of proof to establish, by a preponderance of substantial evidence, the concurrent existence of the following four factors, namely: Duty ⇄ Dereliction ⇄ Proximate Causation → Injury. If he fails to offer such evidence in respect to any of these four necessary ingredients, he fails to establish a *prima facie* cause of action. In that event, the defendant on timely motion is entitled to have the trial court instruct the jury to return a verdict against the plaintiff and in favor of the defendant. If this be done, and judgment is entered on the verdict and thereafter becomes final, the plaintiff is forever barred from further maintaining an action for the same alleged grievance. It is obviously pertinent to our theme, to consider what bearing each of the four terms mentioned may have on the making out of a cause of action for nervous shock. To this end we shall consider each term in seriatim.

A. Duty-Dereliction.

1. *Basis of liability and standard of care.* Duty and dereliction are so closely linked in the law of torts that they are logically like reverse faces of the same coin. It is convenient, however, to think of duty as the pervasive obligation which every member of society owes to avoid creating a substantial risk of injury to those whom he knows or should know are within his sphere of action. It is helpful to characterize this surrounding orbit as the circle of risk. No individual owes a duty to act in respect to another person unless such obligation has been cast upon him by a preëxisting contract or special relationship. In the usual negligence case, where actor and person acted upon are strangers, we are not able to find a preëxisting special duty, and it is necessary to plaintiff's proof of a cause of action that he show some affirmative conduct creating an unreasonable risk of injury to persons of plaintiff's class. In defining what is negligent conduct and what is due care, we take as our standard of reference what the average prudent man would have done under like circumstances.

a. What degree of protection shall the law vouchsafe to the idiosyncratic or excessively vulnerable person? Society has an interest in promoting legitimate enterprise and in encouraging the prime mover. It is also interested in protecting, by way of restitution through money awards, persons who may be injured by the conduct of the actor. These competing interests

are of distinct materiality in the law of torts, which in the last analysis is concerned with placing the risk of loss or injury equitably as between plaintiff and defendant.[49] The law of torts makes use of the concept of culpability or fault, as contrasted with mere causation in determining whether the actor shall make compensation to the person acted upon. Culpability may consist of intentional wrongdoing, and thus partake of a malicious character, or it may consist only of negligence akin to inadvertence. The person acted upon may possess either an average constitution, or he may be an idiosyncratic person who reacts excessively to minimal stimulation. The test of whether an actor, in exercise of due care,* should foresee the likelihood of some injury to another person in the circle of risk must also take into account the nature of the stimulus or conduct and its adequacy to produce injury under normal circumstances. It is only where the actor has reason to foresee some injury to others in his environment that we can justly expect him to abstain from going forward with his legitimate affairs, or can equitably place any liability upon him to pay for injury to others.

It is fair, in our opinion, to hold that an actor has no greater duty of care to one who is idiosyncratic or excessively vulnerable to injury than he owes in respect to normally constituted persons, unless he knows of the idiosyncrasy in advance, or commits an intentional wrong rather than a merely negligent act.

(1) *If the psychic stimulus created by the defendant actor would not have effected an injurious response in a person of normal constitution, there is no breach of duty to one whose injury flows from an idiosyncrasy unknown to the actor.*

Example: D, a woman, had gone to the home of P to help pick and can peaches. A difference of opinion arose between the pickers as to what peaches should be used. In connection with this dispute, D went into the house where P was in bed, and according to P's version, D "wilfully talked in a loud voice and in an angry manner with divers persons in the hearing of the plaintiff." D was unaware that P had been subject to hysteria in times past and was hypersensitive. P sued D, alleging that her loud and angry address had caused P to have hysterial spells on the day in question and one about every 30 days thereafter. P recovered verdict and judgment in the trial court for $100.

Held, on appeal: Judgment reversed; P cannot recover for the reason that D breached no duty of care to her, having no ground to anticipate that P would react excessively to a stimulus innocuous to an average person. Furthermore, "the injury in question not being one which the defendant could reasonably be expected to

---

[49] In connection with this argument for limiting extent of tort liability to idiosyncratic or hypersensitive persons, in respect to mere negligence, see SMITH, H. W., and SOLOMON, H. C.: Traumatic neuroses in Court, *op. cit. supra* fn. 13. See also POUND, R.: Interests of personality, 28 Harvard Law Rev. (1915) 343, 445.

* Due care is defined by an *objective* test, namely: Did the actor use that degree of care (care, diligence, skill and judgment) which the average prudent man would have used under the same or similar circumstances to avoid creating risk of injury by his conduct to those persons or things within range of the peril, whose presence he knew or should have foreseen prior to indulging his conduct?

anticipate as likely to ensue from her conduct, we cannot regard it as the natural consequence thereof for which defendant is legally responsible."

Haas v. Metz, 78 Ill. App. 46 (1898).

(2) *If in advance of the action the actor becomes aware of the idiosyncrasy of some person in the sphere of action, or should know of it, the ordinary duty to use due care may require the actor to abstain from creating or continuing a stimulus which would not hurt the normal person but carries a substantial risk of injury to the vulnerable individual* (see footnote 67, post).

(3) *If the defendant commits an intentional invasion of the plaintiff's rights of personality, he assumes the risk of special vulnerability of the person acted upon.* In this situation, the actor "takes his victim as he finds him" for the reason that the law has no cause for balancing interests or making concessions on behalf of the actor.

Example: Defendant, while in his own house, fired several shots through the lighted window of plaintiff's apartment. P had given birth to a child a few minutes before and was in a hypersensitive condition, unknown to D. She was not struck but she reacted violently and suffered extreme fright, nervous shock, and hysteria, resulting in serious illness. P sued D, but the trial court dismissed the petition on the ground that the New York rule laid down in Mitchell v. Rochester Ry. Co., 151 N. Y. 107, 45 N.E. 354 (1896), denies recovery of damages for injury due to nervous shock or fright unless the plaintiff can prove a contemporaneous impact.

Held, on appeal: Judgment reversed. The defendant indulged willful and wanton conduct, whether it be technically characterized as an assault or not. For injuries sustained thereby as a result of fright, P is entitled to recover her full damages. The Mitchell case applies only to accidents based on negligence, and not to cases of willful tort.

Beck v. Libraro, 220 App. Div. 547, 221 N. Y. Supp. 737 (1927).

(4) *If the conduct is negligent in creating a risk of injury to normally constituted persons, the idiosyncratic individual is allowed to recover full damages for his excessive response, excluding, however, any allowance for preexisting impairment.*

2. *Test of culpability in the nervous shock cases.* Not only is it important to consider whether the culpability involved an intentional and malicious act or mere negligence, and whether the person affected was of normal or idiosyncratic constitution, but one must take into account the adequacy of the stimulus. It is believed that in many of the negligence cases involving nervous shock, the trial courts have not made the importance of this factor sufficiently clear to the jury. The trial court should charge the jury at the conclusion of the evidence that the psychic stimulus created must be such that the actor should have anticipated that he thereby created an unreasonable risk of injury to a person of normal constitution situated within his sphere of action, whose presence he knew or should have apprehended. In many of the nervous shock cases the alleged stimulus is patently inadequate to cause a response in a person of normal constitution.

In other cases the actor has simultaneously, by the negligent operation of a railway locomotive,[50] of a street car,[51] or in the handling of other dangerous instrumentalities, threatened the plaintiff with immediate bodily harm of a serious character, jeopardizing life or limb. The stimulus presented is patently adequate to create the strongest feelings of fright and other deep emotional disturbances in a normally constituted person.[52]

It is important to realize that practically always the stimulus can be analyzed in terms of its sufficiency or insufficiency to create a strong emotional reaction in an average person. This inquiry must always be taken into account in determining whether there has been such breach of duty in the creation of risk of injury as constitutes negligent dereliction.

A problem which has been considerably discussed by law writers and courts is how far the actor has a duty to bystanders, or to persons concealed in houses whose visual, auditory or tactile perception of a suddenly created stimulus engenders injurious fright. We think that since the right of any injured plaintiff to recover damages in the law of torts in cases of the negligence class, depends upon culpability, no recovery can be had by a person unless the defendant actor knew or should have known of his presence within the circle of risk at the time of creating or continuing an unreasonable, potentially harmful stimulus. It is believed that in practice the courts are following this limitation upon liability.[53]

Example a: Plaintiff may be outside the circle of risk because the defendant's stimulus does not come near enough to threaten any bodily harm to plaintiff.

Defendant railway company (D) built a switch from its main track at a point directly across the street from a house and lot owned by plaintiff (P), an

---

[50] As in Victorian Railways v. Coultas, supra, and Bell v. Great Northern Ry. Co., supra. See, also, the many cases against railroads cited in footnotes 7 and 8, supra.

[51] As in Kisiel v. Holyoke St. Ry. Co., 240 Mass. 29, 132 N.E. 622 (1921); Sundquist v. Madison Rys. Co., 197 Wis. 83, 221 N.W. 392 (1928) etc.

[52] Inadequacy of stimulus .to produce the result in a person of average constitution was regarded as a proper ground for denying liability in the Scottish case of Cooper v. The Caledonian Railway Co., IV Session Cases (1902). Plaintiff alleged she suffered nervous shock from a carriage door swinging open and having its window broken. She was never for a moment in the smallest danger of injury. The trial judge reached this conclusion from the pleadings, without evidence and dismissed the case. The appeal court agreed that the stimulus, to be actionable, would need be one capable of producing an injurious response in an average person, but held evidence should have been received on this issue, and remanded the cause for hearing.

In Newton v. New York, N. H. and H. R. Co., 106 App. Div. 415, 94 N. Y. Supp. 825 (1905), X was commuting to New York on defendant's train when it negligently stopped in a tunnel with the result that a train following behind struck it. It was alleged that X suffered nervous shock which four months later caused him to die of acute dilatation of the heart. X's legal representatives, in an action against the RR recovered verdict and judgment for $12,500. Held, on appeal: Judgment reversed because there was no proof that the stimulus caused either physical injury or immediate nervous shock. The evidence showed that when the collision occurred, X was playing cards in a forward coach, and the tremor of impact was so minimal that X was merely moved forward slightly, not thrown against the seat ahead or onto the floor. The players continued at cards without their game board being thrown from their laps.

[53] The only exceptions seem to be occasional cases where courts have held an intentional wrongdoer liable for injury to one he could hardly have expected to be present.

adult female. Due to want of an adequate bumping post at the end of the track, D backed several cars over the end of the switch out into the street in the direction of P's house, but stopping 15 feet away from her yard. P alleged that she saw the spectacle from her house and suffered injurious fright in consequence, for which she sought to hold D in damages. The trial court sustained a demurrer to P's petition on the ground that the facts pleaded did not make out any legal cause of action. P appealed. Held: Affirmed, but, said the court, a right of action might have existed had D's cars rolled into P's yard thereby effecting a wrongful trespass.

     Morse v. Chesapeake & Ohio Ry. Co., 117 Ky. 11, 77 S.W. 361 (1903).

Example b: Plaintiff may be outside the circle of risk because she is a detached spectator remote from the scene of action and so not within any duty of care owed by defendant as actor. In the field of ordinary negligence, we only hold the actor to abstain from creating unreasonable risks of injury to persons whose presence he knows or should apprehend.

     (1) Plaintiff, while perfectly secure in her house, and not exposed to any personal peril, saw through her window the distressing spectacle of defendant's dog mangling her pet cat. Plaintiff sued defendant for negligently permitting his dog to escape custody and come onto her property, alleging that the episode caused shock and distress of mind leading to personal injury. P recovered verdict and judgment against D for $100 in the trial court.

     Held, on appeal: Judgment reversed. In New York, under the rule of Mitchell v. Rochester Ry. Co., 151 N. Y. 107, 45 N.E. 354 (1896), a plaintiff who seeks to recover damages for negligently caused fright must prove a contemporaneous impact; here there was none and P was even far removed from the scene of action. P cannot recover damages. Buchanan v. Stout, 123 App. Div. 648, 108 N. Y. Supp. 38 (1908).

     (2) In Nuckles v. Tennessee Electric Power Co., 155 Tenn. 611, 299 S.W. 775 (1927), plaintiff, while not in range of personal peril from the dangerous conduct, suffered shock and injury from seeing his son run over through D's negligence. Held: P could not recover damages. (Note carefully that Tennessee is one of the states which allows recovery for nervous shock without proof of contemporaneous impact.)

     A further question has arisen as to whether the threat of injury which causes fright or emotional upset need be to the person of plaintiff, or one of his loved ones,[54] or whether it is sufficient if the plaintiff's apprehension is

---

[54] D, by negligent operation of his automobile, frightened P's mule so that it ran away. P was not in the buggy, but suffered great shock and consequent physical injury because of fright for her two children who were in the buggy. Held: P could recover damages from D. Spearman v. McCrary, 4 Ala. App. 473, 58 So. 927 (1912).

     D negligently ran his truck into the basement of P's house. P suffered no impact, but because of fright for safety of his children who were in the basement, he sustained severe shock which led to a hysterical condition. Held: P could recover damages from D. Bowman v. Williams, 164 Md. 397, 165 A. 182 (1933).

     On similar facts recovery was allowed for parental fright generated by apprehension of immediate bodily harm to children, in Hambrook v. Stokes Bros., 1 King's Bench (Eng.) 141; 94 L. J. K. B. 435 (1925), and in Cohn v. Ansonia Realty Co., 162 App. Div. 791, 148 N. Y. S. 39 (1914).

     Courts in America have tended to put limits on liability in this series of cases by requiring the parent to be personally present within the circle of risk; if the parent suffers nervous shock as a mere spectator while situated outside the zone of peril, recovery of damages for nervous shock caused by defendant's conduct is denied. Waube v. Warrington,

for safety of his property whose immediate destruction is threatened by the defendant's conduct. The courts have reacted variously to this problem.[55]

B. Proximate Causation.

In times past there has been an unfortunate tendency in law to encrust concepts of actual or scientific causation with many metaphysical rules or principles. A leading example of this is the insistence of courts in many states that an act or omission cannot be the proximate cause of a particular event unless the result which actually happened was a "natural and probable" consequence. Such an idea is indeed foreign to realism, and as might be suspected, it is used by appeal courts as a mere device to enable them to deny existence of liability where it seems unconscionable or inequitable to make the defendant bear the risk of the particular loss of which the plaintiff complains. Actually what the courts mean when they use the above formula is one of two things:

1. The defendant cannot be connected with the transaction in a culpable relation if an average prudent man could not foresee the risk of injuring another by indulging such conduct. Analytically it would be better to bring

216 Wis. 603, 258 N.W. 497 (Mother, looking through window, saw daughter crossing street killed by D's negligence.)

Accord: Nuckles v. Tennessee Electric Power Co., 155 Tenn. 611, 299 S.W. 775 (1925).

In Hambrook v. Stokes, supra, the English courts allowed a parent to recover damages for nervous shock caused by apprehension that a child on the way to school had been injured by a runaway lorry which rolled down a long hill when the driver negligently left it without the brakes set. The parent here was not in peril of personal harm, and the decision has been criticized as extending liability too far. It may be argued on facts of the case that the presence of the parent in the vicinity was known or could be anticipated and that a parental fright reaction was foreseeable.

If the parent is entirely absent from the scene of action, and reacts only as the result of an after report, the risk of injury seems too remote to be chargeable against the actor.

[55] Most courts, to draw limits of liability in the "nervous shock" cases consonant with their views of policy, have made it an arbitrary requirement that the fear be for self or family and not for property. See Waube v. Warrington, 216 Wis. 603, 608, 258 N.W 497, 499 (1935) ; Dulieu v. White & Sons, (1901) 2 K.B. 669.

In a recent Nebraska case, however, the court declined to impose such limitations on liability and permitted recovery of damages where nervous shock was engendered by concern over a dairy herd poisoned by bran negligently sold by D to a dairyman, X.

The facts were quite interesting. D, a farmer, having forgotten that he had put arsenic in bran for the purpose of poisoning grasshoppers, sold the bran to X. X fed the bran to his cows and the next morning milked them and made deliveries to customers. Late in the forenoon five cows died and five others were made sick. X allegedly suffered severe nervous shock from injury to his herd and fear that he would lose his dairy business, and from apprehension that customers, whom he promptly notified, might suffer arsenious poisoning. X was unable to work after this episode, due to impaired health, and died nine months later of a decompensated heart. There was medical testimony that this was caused by an excessive emotional disturbance. (Note great danger of imposition: Could death from cardiac decompensation be scientifically attributed to nervous shock as cause, particularly in face of a nine month interval between stimulus and alleged response?!)

X's widow sued D for negligently causing death of her husband and injury to the dairy business. The Supreme Court of Nebraska upheld a recovery for both items, by a five to two decision. Rasmussen v. Benson, 133 Neb. 449, 280 N.W. 890 (1938).

It is doubtful whether many American courts will permit recovery for injury due to fright or shock engendered by a negligent act which threatens harm only to another's property, unless the conduct also carries a foreseeable risk of personal injury. Serious doubts must also be voiced, from a scientific point of view, about existence of any actual cause-effect relationship in the Rasmussen case between emotional upset and cardiac decompensation nine months later.

in this type of consideration under the heading of dereliction, and to say that lack of foreseeability of any harm prevents the conduct from being negligent.   Probably the courts have not done this because it has been traditional practice to submit the question of negligence to the jury, and a jury finding on conflicting evidence is final.   The question of causation also is submitted to the jury, but the appeal courts have developed the practice of overthrowing the verdict and reversing the judgment, if in their opinion the result was not "a natural and probable consequence of the defendant's act."   This enables the court to refuse liability despite the jury verdict, in cases where it thinks public policy is opposed to undue extension of liability.

2. The court may mean in holding that the injury complained of is not the "natural and probable consequence" of the defendant's act, that the whole injury, in type, was so bizarre and unusual as to be a remote possibility in the expectation of any reasonably prudent actor. This, too, could be referred analytically to the duty-dereliction terms and made a circumstance tending to prove that there was no negligence.   It could even more accurately be considered under the term "damages," and liability excluded on the ground of remoteness, which technic would merely indicate the appeal court's opinion that public policy was opposed to extending liability so far.

The reader will see that courts in the main are concerned with using devices for placing the risk of loss or injury equitably as between actor and person acted upon in a given species of case.   It is not surprising that the courts use all four terms of the liability formula (duty $\rightleftarrows$ dereliction $\rightleftarrows$ proximate causation $\rightleftarrows$ injury) like keys of a piano board.

In the nervous shock cases some appeal courts have weeded out the more extreme, bizarre cases and denied liability, on the ground that the nervous shock or injury was not the "natural and probable consequence" of the defendant's conduct, so that there was a failure of causation.[56]

We think it would be much better, however, to keep the term "proximate causation" as simple as possible and to use it in the sense of "actual causation." · This would conform legal practice to scientific truth, and clear away much confusion that has arisen in times past from loose and varied usage of the concept of causation in the liability formula.

Heretofore we have considered the mechanisms involved in psychic stimulation and the effects and diseases which might be engendered thereby. It will be necessary in time to explore further by adequate scientific studies

---

[56] Mitchell v. Rochester Railway Co., 151 N. Y. 107, 45 N.E. 354 (1896). (One ground for denying recovery for abortion allegedly caused by fright without impact, when D's horses were negligently permitted to all but run down plaintiff in the street. Two other grounds were given for refusing a right of action: (1) policy argument: difficulties of proof and likely encouragement of fictitious suits; (2) since there can be no recovery for fright negligently caused, there can be no recovery for physical consequences of fright. This last deduction has been widely attacked as specious.)
Miller v. Baltimore and Ohio RR. Co., 78 Ohio St. 309, 85 N.E. 499 (1908). (As in Mitchell case, supra, one ground for denying recovery for injury due to fright, negligently caused, but without contemporaneous impact.)

the relationship of psychic stimulation to all the diagnosable disease entities and syndromes.

At this time we should like to lay down certain orientating principles which might be useful in appraising particular medico-legal claims:

(1) In the usual tort case, the injury claimed by the plaintiff is attributed to a *single* frightening stimulus of fairly short duration. Cases of repeated exposure to the fear-producing stimulus negligently created by defendant arise only rarely, such as continued blasting operations over a period of weeks or months, where large stones continue to be thrown on the roof of plaintiff's dwelling.[57]

The physician must consider whether a causal connection can be postulated between the single stimulus of described severity and the alleged consequential injury or disease. In more than one case which has come before the courts in the past, the plaintiff has had a silent interval with no substantial symptoms, lasting for days, weeks or months separating stimulus and alleged response.[58] Knowing as we do that the immediate physiological changes engendered by fright tend to subside and pass away fairly quickly when the efficient stimulus is removed, long silent periods with no "bridging symptoms" must be looked upon with grave doubts when an effort is later made to establish a causal connection. The bridging symptoms may consist of immediate prostration with various symptoms, such as immediate and persistent pain, or of radical alterations in the behavior pattern, as we find in the so-called traumatic neuroses.

---

[57] Green v. T. A. Shoemaker & Co., 111 Md. 69, 73 Atl. 688 (1909), 23 L. R. A. (N. S.) 667.

[58] A good example is the New York case of Hack v. Dady, 134 App. Div. 253, 118 N. Y. Supp. 25 (1909). Plaintiff, a pregnant woman, was walking along a city street with her two children when negligence of defendant in laying a main caused an explosion in a pot of molten lead. A few drops of the molten lead were cast upon P's hand and clothes, but she quickly flicked them off and suffered only a small superficial burn. P sued D, claiming that fright and nervous shock caused a miscarriage to occur three and a half weeks after the accident, a second miscarriage six months thereafter terminating a two months' pregnancy, and a third miscarriage three months after the second terminating a three months' pregnancy. On the first trial, Dr. A testified positively that these injuries were due to psychic reactions engendered by fright. P recovered verdict and judgment in the trial court, but this was reversed on appeal on the ground that the New York requirement of impact as a prerequisite to recovery for nervous shock, is not satisfied unless the impact contributes substantially to production of the nervous shock or the final injury (miscarriage).

On a second trial, P called Dr. B instead of A. B testified positively that the miscarriages were due to physical injury caused by the spark landing on P's hand. P recovered verdict and judgment for $2000, and on appeal this was affirmed.

This case illustrates the imposition which may occur in this species of litigation. It is characteristic of a large group of cases where:

(1) The minimal trauma was too slight to produce a miscarriage.
(2) The trauma was to a remote part of the body rather than to the abdomen.
(3) There was not a sufficient frightening stimulus to prove psychic miscarriage.
(4) The long time interval of three and one half weeks without proof of bridging symptoms speaks almost conclusively against causal relationships of either trauma or psychic influences.
(5) The history of the case strongly suggests that the repeated miscarriages were due to some independent cause unrelated to D's negligence.

There is a notable exception to the expectation of immediate reaction. It has been observed that when men are under sudden and great emotional stress, as in shipwreck, the final reaction is delayed, oftentimes until after the person so exposed has been put ashore and has gone inland. The inference to be drawn from this phenomenon is that "time for deliberation or contemplation" must be allowed for in reckoning what the final total reaction will be. If the person has gone far beyond such period without appearance of any symptoms, and at a later date claims a disability from his frightening experience, it is proper, unless there be very exceptional proof, to deny the causal connection.

(2) The test of injury is not a mere transient invasion of mental tranquillity speedily passing away, but whether or not we can say scientifically that the stimulus produced some disability in the form of temporary or permanent or partial or total incapacity for continuing usual pursuits. Needless to say, pain and the like are compensable as separate items, in addition to any physical injury and loss of time from work.

(3) If the plaintiff be subjected to some frightening stimulus which causes no injurious effect or disease, but after a substantial interval of time he begins brooding over what might have happened and thus becomes disabled by neurosis, this is held by the law not to be compensable.[59] It is believed that this view is sound, because when the interval is so long, independent factors may be operative. Though there may be actual causation in a particular case, it is defensible for the law to find a failure of causation on grounds of policy and the conjectural character of the evidence.

(4) *Proof of malingering.* Malingering may have two different legal effects, namely:

a. If the claimant has suffered no injury at all and his claim is a pure fabrication, proof of this, if credited by the trier of fact (the jury, or the judge if there be no jury) defeats the right to recover *any* damages, by disproving existence of the terms *causation* and *injury* of the liability formula.

b. If the plaintiff has suffered some genuine injury, but is malingering

---

[59] Swift & Co. v. Ware. (Ga. Appeal), 186 S.E. 452 (1936).

Phelps Dodge Corporation v. Industrial Commission, 46 Ariz., 162, 49 P. (2d) 391 (1935). X, a miner, ran 500 feet to reach fresh air after blast of a "missed hole" caused shafts and drifts of the sulphide ore mine to become filled up with smoke, gas and dust. He suffered no injury but thereafter developed a neurosis from brooding over what might have happened to him, and in that event what would have been the lot of his family. Held: Since the neurosis was not caused by nervous shock produced by the episode, but by subsequent brooding, the neurosis was not result of an *"injury"* sustained by accidental means, and was not compensable under terms of the Arizona Compensation Act.

In certain interesting cases claim has been made under Workmen's Compensation Acts for suicide due to insanity allegedly caused by an accidental injury received in course of employment. Courts have held it is not enough that insanity was indirectly caused by the injury if the more immediate cause was worrying and fear of losing employment (Grime v. Fletcher [Eng. 1915], 1 King's Bench 734; 8 B. W. C. C. 11, C. A.) or depression and brooding over inability to work. (Withers v. London, Brighton and South Coast Rail Co. [Eng. 1916], 2 King's Bench 772, 9 B. W. C. C. 616, C. A.)

There may be *actual causation* here, but it must be admitted that lapse of time, the entry of independent causes, and difficulties of proof, justify the law in drawing an outer line of liability, though somewhat arbitrarily, in this type of case.

as to the extent of symptoms or duration of disability, proof of these facts will not destroy the cause of action, but will only operate under the term "injury" in the trial formula to reduce the amount of damages recoverable.

Probably malingering of the first type is rather rare. It is rather dangerous in point of trial strategy for defendant to try to prove malingering, unless he can set his contention up with considerable strength. To create a mere suspicion of malingering usually acts as a boomerang, for one needs to impute a fraudulent intent to the plaintiff, and a jury deeply resents the making of such charges without strong proof. These considerations account partially for the infrequency with which lawyers raise malingering as a defense in the nervous shock cases.

We feel it necessary, however, to make some allusion to malingering, and we do so under two headings, namely:

a. Proof of malingering by lay investigation and testimony. Insurance company adjusters, claim agents, or specially retained detectives are often able to observe the claimant when he is acting spontaneously and completely unaware that he is being watched. A person who claims to be paralyzed may walk; one who uses crutches may cast them aside; one who is kept constantly in bed in a state of prostration may be seen vigorously cleaning house; various neurological symptoms may disappear. Sometimes it is possible for the observer to take motion pictures, and the courts have held that these may be shown in evidence. Obviously lay evidence of this variety depends upon producing a flat contradiction so that the claimant is made out a complete liar.

b. Medical proof of malingering. The doctor must apply his common sense as a layman, as well as his special medical talents. In many cases it will be found that the case falls in class b, where there is some genuine disability which the patient is exaggerating, oftentimes by the process known as "unconscious" malingering. Usually a more just result can be reached by considering such factors as evidence of preëxisting impairment of personality, under the term "injury" of the trial formula, and discounting the amount of damages accordingly which one would attribute to the accident itself.

It is held that a doctor who has examined a claimant is entitled to give his opinion that he is a malingerer,[60] and that even without benefit of such examination he may give his opinion after observing the claimant on the witness stand.[61]

Hysteria and malingering. Distinguishing hysteria and malingering is one of the recurrent problems, and so we single it out for special attention.

Hysteria, using the word in the narrow and technical diagnostic sense,[62] is a disorder associated with childish behavior. Not only is the behavior

---

[60] Klein v. Medical Building Realty Co. (La. App.), 147 So. 122 (1933).
[61] St. Louis, I. M. & S. R. R. v. Osborne, 95 Ark. 310, 120 S.W. 537 (1910).
[62] LINDEMANN, E.: Hysteria as a problem in a general hospital, Med. Clin. North Am., 1938, xxii, 591.

childish, but the patient often looks younger than her years and may have a childish build and under-developed organs. The typical cases have symptoms that are almost naïve in their obviousness: a bride loses her eyesight when her husband is ordered to sea duty; a boy has "fits" when his father and mother quarrel; a young married woman who does not want any more children develops spastic adduction of the legs. These patients show such symptoms with *"belle indifference"*; they do not worry about the symptoms. They do not, however, see the connection between the situation they are in and the symptoms. The primitive, childlike idea "I can't stand it, so I'll be sick and get out of it" was probably in their heads, but they discarded it, acted on it and forgot it. This is the mechanism known as conversion with amnesia. The childish and unworthy thought is converted into action, the unbearable situation is converted into protective invalidism. The amnesia is childish in its simplicity and completeness. Under hypnosis and by associations such mechanisms can sometimes be brought to light; explanation often cures. If not, a shrewd "putting of the shoe on the other foot" by the physician causes the symptom to disappear.

Such in a simplified schematization is the mechanism of hysteria. Why is it not malingering? Where is the line? Can it be drawn?

Malingering is willful and conscious falsification. Symptoms are imitated with an ulterior motive. The simple cases, such as men who escape army duty by eating soap, are easy enough to understand. But others are not so simple. For example, a woman slipped on some garbage on the stairs of a railroad station; falling, she fractured her coccyx and was taken to a hospital. Here roentgenograms showed the injury. In a few days she returned home well. Here she was apparently happy until a lawyer asked her a lot of questions and suggested to her the possibility of getting damages from the railroad. She returned to the hospital in a wheel chair, said her legs were weak and painful and talked about law suits. The diagnosis this time was "malingerer" and a mental test showed her to be a moron (mental age about nine years). She was sent home. Six months later she returned to the hospital with stiff, weak legs and anesthesia up to the thighs. The examiner could put pins into the skin and muscle without hurting her. The muscles showed atrophy from disuse. This time the diagnosis was "hysteria." In her moronic mind she had made the conversion and forgotten it. Starting as a rather stupid malingerer she had become an automatic hysteric.

It is obvious that a line cannot be drawn in some cases. Many cases of hysteria start with more or less conscious wishes for a symptom to gain an end. Some malingerers are so obvious and simple that they are to be classed as feeble-minded, others are smart but deceitful to such a degree that they are psychopathic. A few are just average folks who are trying out an acted lie. The differential diagnosis takes a man not only with psychiatric experience, but shrewdness. Each case must be studied thoroughly and individually.

C. The term "injury" in the trial formula and pertinent doctrines of the law of damages.

If the defendant was guilty of a willful, intentional invasion of plaintiff's rights of personality, as for instance committing an "assault" by creating an immediate apprehension in plaintiff of immediate bodily harm, this gives a technical cause of action for some damages, even though no actual harm was suffered.[63]

Very few of the nervous shock cases fall in this category, but depend on allegations of negligence, and such cases cannot be maintained in court without proof of actual injury or damages. The plaintiff is entitled to recover for physical and mental pain and suffering past and future, for any physical injury itself, for medical expense, and for loss of earnings.

It is characteristic of the many "nervous shock" cases that the response to the particular stimulus is quite excessive, more than that which a person of average constitution would give. The stimulus may be the mere occasion or circumstantial cause of the response when preëxisting factors constitute the substantial cause. In science we are accustomed to sorting out all the contributing causes and allotting a just share of responsibility to each factor. The law has developed on a cruder basis, not apportioning causation as such, but holding that an actor is or is not a substantial cause of the injury; if so, he is liable for the whole injury, if not, he is legally responsible for none of it. In the main, this "all or none" way of treating causation does not work great injustice, but it falls down when a $100 impact produces a $10,000 injury because of idiosyncrasy of the plaintiff. What can be done to rectify this situation, is a major problem discussed elsewhere.[64] For one thing, a defendant must be alert to prove that the disability in large part represents a preëxisting impairment, for which the plaintiff cannot recover damages, rather than mere excessive injury due to the accident itself operating on a vulnerable person. In the latter case, American courts allow full compensation because of their refusal to apportion causation.[65]

[63] Usually it is said the actor must have the apparent means of "then and there" converting threat into injury; hence, it is necessary that the actor be close at hand, and a threat made at a distance, by telephone, would not be sufficient to constitute an "assault." If injurious fright were caused by such a "long distance" threat, the right to hold the speaker in damages might well turn on these questions:

(1) Did A, in speaking, maliciously intend to cause B harm through fright? If so, A should be held liable in damages.

(2) If the answer to (1) is "no," A's right to recover damages must depend on proof of negligence:

a. Did A know that B was idiosyncratic or excessively vulnerable and so apt to be caused injurious fright by the threatening language? If so, A should be held liable in damages.

b. If A did not know of any idiosyncrasy, should he have foreseen that his verbal conduct would be likely to cause injurious fright in a listener of average constitution? If so, A should be held liable in damages.

[64] See SMITH, H. W., and SOLOMON, H. C.: Traumatic neuroses in Court, in Smith on Scientific Proof and Relations of Law and Medicine, Matthew Bender & Co., Albany, N. Y. (In press).

[65] See, for instance, Flood v. Smith, 126 Conn. 644, 13 A (2d) 677 (1940). As the result of an automobile collision caused by negligence of D, P₁ and P₂ sustained injuries in excess

On the other hand, there is now respectable authority, which is doubtless destined to become the universal rule, that where medical testimony can separate out that part of the injury due to the accident, and that part due to preëxisting causes or idiosyncrasies, the plaintiff can recover damages only for the first.[66]   As we have said, the case may be otherwise where the actor knows or should know of the other person's preëxisting disease or idiosyncrasy,[67] for here the duty of due care may be held to require more cau-

of those which an average person would have suffered from a like stimulus. Proof showed that P_1, a 28 year old man, two years previously had been injured in another automobile accident, suffering a fracture of his skull and impairment of his nervous system, but with substantial interim recovery. P_2, his companion, was a 70 year old library cataloguer, who previous to the accident, had suffered two nervous breakdowns and had undergone surgery for the removal of a cancerous breast. Both P_1 and P_2 were bruised in the accident and suffered extreme nervous shock, in P_2's case aggravated by her morbid fears that a bruise on the site of the amputated breast would reactivate her cancer. The jury awarded P_1 $3500 and P_2 $4100. The trial court thought these damages excessive and granted D's motion to set aside the verdict and order a new trial unless P_1, by remittitur, relinquished $1275 of the verdict, and P_2 $2027. P_1 and P_2 appealed.

Held: The damages awarded by the jury were not excessive. Cases remanded with orders for trial court to enter judgment for the full verdicts.

The Connecticut Supreme Court said: "The plaintiffs are entitled to recover full compensation for all damage proximately resulting from the defendant's negligence, even though their injuries are more serious than they would otherwise have been because of preëxisting physical or nervous conditions."

It is submitted that the result of this case is wrong, for it imposes a liability for a total end result only partly caused by the defendant's stimulus.

[66] Moore v. Tremelling (U. S. Circuit Court of Appeals, Idaho), 78 F. (2d) 821 (1935); same case, on later appeal, 100 F. (2d) 39 (1938).

X fractured his leg and retained surgeon Y to treat it. As a result of negligent failure to take post-reduction roentgenograms at intervals after properly setting the fracture, Y failed to discover that the bones had slipped out of apposition. X developed a bad end result. Held: X could recover compensatory damages from Y for the result of his malpractice but not for such part of the end result as would have been due to the original fracture properly treated. The burden was on X to separate out the two items of damage.

In certain recent Workmen's Compensation cases, it has been held that in assessing damages, causation should be apportioned between accident and preëxisting factors: Ashland Limestone Co. v. Wright, 219 Ky. 691, 294 S.W. 159 (1932).

The same result has been reached by reducing the percentage of total disability which would be allowed if the accident were the sole cause: Moray v. Industrial Commission of Utah, 58 Utah 404, 199 P. 1023 (1921); Sykes v. Republic Coal Co., 94 Mont. 239, 22 P. (2d) 157 (1933).

This meticulous apportionment between accident and preëxisting causes is a new trend which is more scientific and equitable than the practice of holding a merely negligent actor fully responsible for injury only partially caused by him.

[67] Defendant Wing was indicted for maliciously discharging a gun, whereby a woman, named M. A. Gifford, was thrown into convulsions and cramps.

Defendant had discharged the gun in a highway, for the purpose of killing a wild goose, at a place not more than two or three rods from the house in which Miss Gifford lived. He asserted that it was his right to fire the gun as he pleased, for the reason that the shooting occurred on a neck of land to which citizens had resorted since time immemorial for the purpose of fowling.

Evidence on the trial proved that Miss Gifford had been severely affected with a nervous disorder for some six years, with the result that she was uniformly thrown into a fit upon hearing a gun, thunder, or any other sudden noise, or by hearing the words *gun*, *ammunition*, etc., mentioned. It was shown that defendant was warned of this fact and requested not to fire the gun, but that he did so nevertheless.

"The [trial] judge instructed the jury, that if they believed that the defendant knew, or had good reason to believe, that the consequences above mentioned would be produced by the firing of the gun, and had notice to that effect immediately before the firing, they should return a verdict of guilty; which they did accordingly. If this instruction was wrong, a new trial was to be granted."

Held, on appeal: Conviction affirmed. Chief Justice Parker of the Supreme Judicial Court of Massachusetts said:

tion. The courts are less likely to sort out damages where the actor is guilty of an intentional battery or other wrongful invasion of the plaintiff's rights of personality. But the result here is best explained on the ground that the actor is a thorough-going culprit, worthy of having punitive damages assessed against him by way of example, so that the court feels no deep concern about apportioning damages with scientific delicacy in his behalf, or weighing out justice on golden scales, as it were.

The physician should go to court carefully prepared by study of the pretraumatic personality of the claimant, and thorough neurological and psychiatric examinations, and a due regard to the nature and adequacy of the stimulus, the immediacy of symptoms and the nature and continuity of disability, to say what portion of the total injury or damages should be allocated to the accident and what part to preëxisting factors. The physician should be very firm in this respect, for the law in many states is now in such condition that this vital distinction is blurred, and grossly excessive verdicts are being entered against defendants for injuries which they only partially caused. It is our opinion that a competent examiner can arrive at a satisfactory estimate in making this apportionment, but that he must individualize each case.

CONCLUSION

We have endeavored in this communication to make certain salient points, as follows:

(1) A study of the nervous shock decisions demonstrates the absence in times past of any adequate criteria for judging actual causation of the alleged injury or disease by the given stimulus.

(2) We saw that the chief stimulus which underlies the nervous shock cases is fright, and the chief disabilities claimed are "nervous shock" with consequential disability, usually temporary; traumatic neuroses; and alleged psychic abortions or miscarriages.

(3) We have given an account of the current concept of "nervous shock," showing in general the mechanism of its production.

(4) We have mentioned those independent diseases, aside from the various neuroses and immediate injuries, for which there is now substantial

". . . we think the offence described is a misdemeanor, and not a nuisance. It was a wanton act of mischief, necessarily injurious to the person aggrieved, after full notice of the consequences, and a request to desist. The jury have found that the act was maliciously done.

"In the case of Cole v. Fisher, 11 Mass. R. 137, Chief Justice Sewall, in delivering the opinion of the Court, speaking of the discharging of guns unnecessarily, says, if it is a matter of idle sport and negligence, and still more when the act is accompanied with purposes of wanton or deliberate mischief, the guilty party is liable, not only in a civil action, but as an offender against the public peace and security, is liable to be indicted, &c.

"Now the facts proved in the case, namely, the defendant's previous knowledge that the woman was so affected by the report of a gun, as to be thrown into fits, the knowledge he had that she was within hearing, the earnest request made to him not to discharge his gun, show such a disregard to the safety and even the life of the afflicted party, as makes the firing a wanton and deliberate act of mischief."

Commonwealth v. Wing (Supreme Judicial Ct. of Mass.), 9 Pick. 1, 19 Am. Dec. 347 (1829).

medical evidence that psychic stimulation may be a causal factor in pathogenesis.

(5) We have stressed the need for continued and systematic study of the relations of all disease states and syndromes to determine what effect psychic stimuli, particularly of sudden and severe character, may have either on production of the condition or upon its activation, aggravation, or acceleration.

(6) We have pointed out that the idiosyncratic or excessively vulnerable person, for reasons of social policy, should not be granted more legal protection against mere negligence of an inadvertent actor, than the person of average constitution receives.

(7) The fact last mentioned, coupled with the recognized fact that emotional stimuli may be mere trigger mechanisms to cause appearance of symptoms of a preëxisting disorder, requires the most careful apportionment of final injury between accident and preëxisting impairment or disease of the subject.

(8) We have endeavored to provide a rationale, both legal and scientific, for study of the existence and extent of liability in the nervous shock cases, sometimes referred to generically as cases of "liability without impact." Here we stress the necessity for remembering the essential terms Duty + Dereliction + Proximate Causation + Injury, whose concurrent existence must be proved by a preponderance of substantial evidence before a plaintiff can establish any right of action.

(9) It is emphasized that with the advance of scientific knowledge, especially in physics, "physical impact" in the sense of striking the person of the plaintiff with a "physical object" becomes meaningless. Waves of air from an explosion may cause "blast injury" or traumatic sounds. Waves of ether may cause visual injury or burns. These involve "physical contact" just as truly as striking the plaintiff with a weapon. By the same token the distinction between "organic" and "functional" disorders has been eliminated. Disorder of function in an organ cannot occur without structural changes in that organ, although these may be temporary. If the law momentarily clings to distinctions between gross and microscopic injury and false distinctions between "organic" and "functional" disorders, it can be justified only by difficulties of proof. This justification should vanish with introduction of proper criteria of proof and of improved mechanisms of trial for handling scientific issues.

(10) We call special attention to the need for studying the stimulus and its adequacy to produce a response in a person of average constitution, as this consideration must be taken into account in determining to what extent the response of the particular patient is due to his idiosyncrasy, excessive vulnerability or preëxisting impairment.

INTRACRANIAL ANEURYSMS—A REPORT OF THIRTY-SIX CASES *

By Nathan Mitchell, M.D., and Alfred Angrist, M.D.,
Jamaica, Long Island, N. Y.

From November 1935 to April 1942, there were observed in the laboratories of the Queens General Hospital 36 cases of intracranial aneurysm affecting the cerebral arteries in a total of 3080 autopsies. The report that follows will describe the pertinent anatomical and some of the clinical features associated with these aneurysms. On the basis of the histopathological findings, an attempt will be made to throw further light on the mechanism of rupture of the so-called "berry" aneurysms.

Numerous excellent descriptions of the clinical syndrome and of particular pathological features of ruptured aneurysms of the cerebral arteries abound in the literature. In a study of cerebral aneurysms by Richardson and Hyland,[1] references will be found to most of the earlier studies. Forbus [2] first showed the frequent association of medial defects in the cerebral arteries and the congenital type of aneurysm. He found the defects at the bifurcation of the cerebral arteries in cases with and without aneurysms. Forbus postulated as the cause of the aneurysms, a congenital defect of the muscular tissue of the media which when exposed to intra-arterial pressure, lead to aneurysmal dilatation and sometimes rupture. Glynn [3] in a study of routine sections of the cerebral arteries in cases with and without aneurysms, found medial defects in 80 per cent of both groups. By means of injection experiments, he found no weakness or bulging at the site of naturally occurring or experimentally produced defects. The latter were produced by sectioning the adventitia and media of the artery and leaving the intima intact. Since the elastica is entirely confined to the intima of the cerebral arteries, he concluded that the weakness of the vessel wall is entirely a function of the state of the elastic tissue. He contended that dire consequences result when atheroma affects the cerebral vessels with consequent destruction of the elastica. He held that medial defects play no part in aneurysm formation. Richardson and Hyland believe that "the medial defects are probably developmental and play a part in causing aneurysms, but that there is another unrecognized acquired lesion which causes degeneration of elastic tissue." In a complete study of 40 cases with intracranial aneurysms, they reported 27 cases with rupture, and 13 cases of unruptured aneurysms. Altogether 53 aneurysms were found in their 40 cases, of which two were arteriosclerotic and the remainder of the congenital "berry" type. They reported an unusually high incidence of intracerebral hemorrhage in their series, describing

19 instances of this complication associated with a varying degree of subarachnoid hemorrhage. Ten of the 19 hemorrhages were located in the frontal lobe, whereas the remaining nine were found in the temporal lobe. The two authors recorded no instances of mycotic or syphilitic aneurysm. Of the latter, the statement is made that "syphilis plays little or no part in the formation of cerebral aneurysms." Concerning mycotic aneurysms, they refer to Turnbull's study, in which 15 of 44 aneurysms were of the mycotic variety. Martland,[4] in a study of fatal spontaneous subarachnoid hemor-

CHART I

Résumé of 36 Cases of Intracranial Aneurysm

Case No.	Age	Sex	Type of Aneurysm	Cause of Death	Duration of life	Remarks
1.	45	M	Berry	Bilateral frontal lobe hemorrhage	Six weeks	Double ruptured "berry" aneurysms of anterior cerebral arteries.
2.	12	M	Berry	Intraventricular hemorrhage	One week	History of falling off bicycle, preceded by dizziness.
3.	46	F	Berry	Subarachnoid hemorrhage	Found dead	Necrosis of wall of aneurysm with polynuclear inflammatory reaction. Polycystic kidneys, cysts of liver; hypertension for many years.
4.	65	F	Arteriosclerotic	Subarachnoid hemorrhage	Found dead	
5.	56	F	Arteriosclerotic	Subarachnoid hemorrhage	Found dead	Large aneurysm measuring 4 cm. in diameter found deep in temporal lobe.
6.	33	M	Mycotic	*Staph. aureus hem.* sepsis	Incidental finding	Medusa-head minute aneurysm of leptomeningeal artery; cavernous sinus thrombosis.
7.	44	F	Syphilitic	Subarachnoid hemorrhage	Found dead	Miliary gummata of kidney; active syphilitic hepatitis with cirrhosis.
8.	42	F	Berry	Subarachnoid hemorrhage	Two days	Blood pressure, 236 mm. Hg systolic and 110 mm. diastolic; hypertrophied heart.
9.	27	F	Mycotic	Intraventricular hemorrhage	More than four hours	*Strep. viridans* subacute bacterial endocarditis.
10.	43	M	Traumatic	Cerebral hemorrhage	Ten days	Trauma to head one month previously; aneurysm connecting internal carotid artery and cavernous sinus.
11.	18	F	Mycotic	Cerebral hemorrhage	? (no definite symptoms)	Picture of cerebral hemorrhage masked by debility associated with *Strep. viridans* subacute bacterial endocarditis.
12.	43	M	Berry	Subarachnoid hemorrhage	Five days	No previous episodes; onset with headache, convulsions.
13.	14 mos.	F	Mycotic	Meningitis	Incidental findings	Influenzal meningitis.
14.	69	F	Berry	Encephalomalacia	Incidental findings	Marked cerebral arteriosclerosis in vessels other than aneurysm.
15.	51	M	Mycotic	*Staph. aureus hemolyticus* sepsis	Incidental findings	Multiple kidney abscesses; multiple small aneurysms of subcortical vessels.
16.	17	F	Mycotic	*Staph. aureus hemolyticus* sepsis	Incidental findings	Multiple kidney abscesses; multiple small aneurysms of subcortical vessels.

CHART I—*Continued*

Case No.	Age	Sex	Type of Aneurysm	Cause of Death	Duration of life	Remarks
17.	73	M	Arterio-sclerotic	Subarachnoid hemorrhage	Five days	Blood pressure 180/100; hypertro-phied heart; marked generalized and cerebral arteriosclerosis.
18.	31	M	Berry	Subarachnoid hemorrhage	Three days	Active sickle cell anemia.
19.	57	F	Berry	Cerebral hemorrhage	Incidental findings	Blood pressure 200/140; syndrome unrelated to aneurysm.
20.	58	F	Arterio-sclerotic	Subarachnoid hemorrhage	Four days	Monckeberg's sclerosis of intra-cavernous portion of internal carotid artery.
21.	14	F	Mycotic	Cerebral hemorrhage	Seven days	*Strep. viridans* subacute bacterial en-docarditis.
22.	58	F	Arterio-sclerotic	Subarachnoid hemorrhage	Six hours	Marked generalized arteriosclerosis.
23.	28	F	Syphilitic	Subarachnoid hemorrhage	28 hours	One previous episode; positive blood Wassermann; active meningo-vas-cular syphilis.
24.	61	F	Arterio-sclerotic	Subarachnoid hemorrhage	18 hours	Moderate cerebral arteriosclerosis.
25.	16	F	Mycotic	Subarachnoid hemorrhage	24 hours	*Strep. viridans* subacute bacterial endocarditis.
26.	45	F	Arterio-sclerotic	Cerebral hemorrhage	Six hours	Unilateral frontal lobe hemorrhage; moderate cerebral arteriosclerosis.
27.	46	M	Berry	Subarachnoid hemorrhage	Found dead	History of hypertension.
28.	48	F	Berry	Traumatic shock	Incidental finding	
29.	56	M	Berry	Subarachnoid hemorrhage	24 hours	Hypertrophied heart.
30.	25	F	Berry	Subarachnoid hemorrhage	Found dead	Small amount of thymic tissue, hy-poplastic aorta and adrenal.
31.	50	F	Berry	Subarachnoid hemorrhage	Found dead	
32.	11	F	Mycotic	Subacute bacterial en-docarditis	Incidental finding	Two aneurysms of convexity of pa-rietal and occipital lobes.
33.	29	F	Berry	Subarachnoid hemorrhage	More than four hours	Red headed; enlarged thymus, hypo-plastic aorta and cerebral vessels.
34.	35	F	Berry	Subarachnoid hemorrhage	10 minutes	Found dead at home 10 minutes after notification of father's death.
35.	52	F	Arterio-sclerotic	Subarachnoid hemorrhage	Found dead	Paget's disease of skull; fracture of skull.
36.	16	F	Mycotic	Cerebral hemorrhage	More than 24 hours	*Strep. viridans* subacute bacterial endocarditis.

rhage in Medical Examiner's material, reported 38 berry aneurysms in a total of 49 cerebral aneurysms. He stressed the fact that fully 2 per cent of sudden natural deaths are due to ruptured aneurysms. Of the 54 cases, 21 were either found dead or died within 30 minutes of collapse, and 41 were dead within 12 hours of the onset of the initial symptoms. Dial and Maurer[5] described seven arteriosclerotic and two syphilitic aneurysms in a series of 13 cases of subarachnoid hemorrhage. In a special article, Mc-Donald and Korb[9] presented the most extensive bibliography and analytical study of 572 cases, with 49.5 per cent arteriosclerotic, 12.2 per cent embolic or mycotic, and only 5.6 per cent syphilitic, with 32.7 per cent listed as nor-mal, the latter ostensibly of the "berry" type.

Material. The cases included in this study represent those encountered in the routine autopsy service of a general hospital laboratory, and a group of cases performed under the direction of the Medical Examiner's office in the County of Queens. Only those cases in which a definite aneurysm or site of rupture was identified are described. Excluded from the reported series are the cases of fatal subarachnoid hemorrhage in which the site of bleeding was not identified; and uniform aneurysmal dilatation of the cerebral arteries demonstrating no discrete aneurysmal sac. Chart 1 lists the material studied, with some of the pertinent clinical and pathological data.

Age and Sex. There were 28 females and 10 males in the series. The ages ranged from 14 months to 69 years, with a mean age of 40 years.

Clinical Features. Of the 36 cases encountered, no previous clinical data are available in 20. Eight of these are represented by incidental findings at autopsy, whereas the remaining 12 were found dead or died before admission to the hospital. Chart 2 outlines the duration of life after onset of symptoms in the 28 cases in which this information was present.

<div align="center">

CHART II

Duration of Life after Onset of Symptoms in 28 Cases

</div>

Found dead	Less than 1 hour	Less than 12 hours	1 day	2 days	3 days	4 days	5 days	6 days	More than 1 week
12	0	4	4	2	1	2	2	0	1

Coma was noted as the presenting symptom in 10 of the 16 cases observed on the wards of the Queens General Hospital. Severe headache was noted as a prominent symptom in five instances; convulsions were seen on four occasions. Less frequent symptoms were stiff neck (3), hemiplegia (2), and dizziness, vomiting, diplopia, and a buzzing sound in the head. The latter was noted in the single instance of traumatic arteriovenous aneurysm of the internal carotid artery and the cavernous sinus.

Of significance was the presence of hypertension in nine cases. Case 34 is of particular interest in demonstrating the influence of emotional upset in the production of hypertension, and its relation to the rupture of the aneurysm in this instance. The patient, a 35 year old white female, was notified of her father's death. Ten minutes later she was found dead in the bathroom.

Pathological Features: Type of aneurysm. In six of the cases, two aneurysms were found yielding a total of 42 aneurysms in the 36 cases of the series. Twenty-two were found at the bifurcation of the vessels of the base and conform to the description of the typical "berry" aneurysm. Mycotic aneurysms were seen in 11 cases. Of the remaining nine cases, six were arteriosclerotic, two syphilitic and one traumatic. The mycotic aneurysms may be divided into two groups. *Streptococcus viridans* subacute bacterial endocarditis provided the septic focus for seven aneurysms. *Staphylococ-*

cus aureus hemolyticus sepsis accounted for three others, and the fourth was seen in a case of influenzal meningitis.

CHART III
Sites of Aneurysm

Middle cerebral artery	10
Anterior communicating artery	8
Anterior cerebral	6
Internal carotid	5
Convexity	5
Basilar	3
Vertebral	2
Posterior communicating	1
Posterior cerebral	1
Anterior inferior cerebellar	1
Total	42

Site of aneurysm. In chart 3 is listed the incidence of the aneurysms on the various branches of the Circle of Willis. Those occurring on the convexity of the brain were invariably of the mycotic type, and were found in each instance incidentally either grossly or on section through a focal area of subarachnoid hemorrhage. It should be stressed that whenever a zone of subarachnoid hemorrhage was seen in a case of meningitis or sepsis, section was taken for microscopic study, thus accounting for a high incidence of mycotic aneurysms.

A method employed by the authors in identifying the site of rupture in those cases where no definite aneurysmal sac was seen in the basilar vessels was suggested by Dr. Richard Grimes, Assistant Medical Examiner, and seems worthy of comment. At times, after careful dissection of the vessels and removal of the entire blood clot cast from the subarachnoid space, a ragged zone was seen in a portion of a vessel with adherent blood clot. If a closed circuit is made by means of clamps, and water is injected under moderate pressure, the site of rupture is then indicated by escape of a thin stream of water. Two instances of rupture of the vertebral artery were demonstrated by this method.

Size. The smallest aneurysm in the series was 2 mm. in diameter, whereas the largest measured 4 by 4 cm. The majority varied from 3 to 10 mm. in size.

Sites of hemorrhage. In each case of ruptured aneurysm recorded, there was seen subarachnoid hemorrhage which varied in amount. In some of the small mycotic aneurysms, hemorrhage of a focal nature was seen usually over the convexity of the cerebrum. In the cases of rupture of the vessels comprising the Circle of Willis, blood clot casts of the subarachnoid space and the cisternae at the base of the brain were seen. In 10 cases *intracerebral hemorrhage* of varying degree was noted. This form of hemorrhage likewise varied from small zones to extensive areas, the largest measuring 8 by 6 by 4 cm. The location of the zones of intracerebral hemorrhage were as

FIG. 2. *Case 1.* Symmetrical bilateral hemorrhage into frontal lobes suggesting slow ooze from ruptured symmetrically placed aneurysms (see figure 1). Note terminal ventricular extension.

FIG. 1. *Case 1.* View of base of brain. Arrow 1 below ruptured "berry" aneurysm of right anterior cerebral artery. Arrow 2 points to symmetrically placed ruptured aneurysm of left anterior cerebral artery. Note limited regional subarachnoid hemorrhage.

follows: frontal lobe (4), temporal lobe (2), basal ganglia (3), and corpus callosum (1). All of the frontal lobe hemorrhages were associated with aneurysms of the anterior cerebral arteries, case 1 (figures 1 and 2), case 2 (figures 3 and 4). The temporal lobe hemorrhages followed a rupture of aneurysms in the middle cerebral arteries, case 5 (figure 8). Intraventricular extension of the hemorrhage was found in 11 cases. One of the 11 cases presented only intracerebral hemorrhage associated with bleeding extending to the ventricles. Five were associated with subarachnoid hemorrhage only, and the remaining five were found in cases showing both intracerebral and subarachnoid hemorrhage.

Associated pathological findings. Hypertrophy of the heart was found in the nine cases which showed evidence of hypertension clinically, or with a history of hypertension. Case 3 presented other congenital anomalies associated with the berry aneurysm. Large polycystic kidneys and multiple cysts of the liver were noted in this instance. O'Crowley and Martland [6] have noted this association of polycystic kidneys with the so-called congenital aneurysms of the cerebral vessels. For the congenital feature to be significant, hypertension should be ruled out. He also stressed the occasional occurrence of status thymolymphaticus. In two of our cases, cases 30 and 33, variable amounts of thymic tissue were found. In case 30, a hypoplastic aorta and adrenal cortex were seen. In case 33 the alleged typical appearance of status was present. The patient was a red-headed, fair-skinned individual with a large thymus and hypoplastic aorta and cerebral vessels. In case 35 the patient had extensive Paget's disease of the skull. The history in this case was of interest for its medico-legal implications. The patient, a 52 year old female, was found dead at the foot of a flight of stairs. A large laceration of the scalp was seen. Upon reflecting the scalp a large linear fracture of the skull was noted. Careful dissection of the brain, however, revealed extensive subarachnoid hemorrhage from a ruptured arteriosclerotic aneurysm of the basilar artery. The two cases of ruptured syphilitic aneurysm of the cerebral vessels were accompanied by evidence of active syphilis of the meninges, cerebral vessels, and brain. In case 7 multiple miliary gummata of the kidney were found in addition to active syphilitic hepatitis with cirrhosis. In case 23 a gross diagnosis of berry aneurysm was made, but microscopy revealed active cerebral meningovascular syphilis and gummatous necrosis of the wall of the aneurysm.

It is noteworthy that of the 11 mycotic aneurysms only three organisms were found on culture in various sites. The *Streptococcus viridans* was found in seven instances, all these cases presenting a classical picture of subacute bacterial endocarditis. The other organisms implicated were the *Staphylococcus aureus hemolyticus* and *Hemophilus influenzae*. In two of the cases the immediate seeding focus for the sepsis was the presence of multiple kidney abscesses. The third case was one of cavernous sinus thrombosis.

FIG. 3. *Case 2.* Base of brain showing massive subarachnoid hemorrhage in inter-peduncular space and about pons with limited extension to cerebellum. Arrow points to site of rupture of "berry" aneurysm of anterior communicating artery.

FIG. 4. *Case 2.* Unilateral frontal lobe hemorrhage suggesting slow ooze from aneurysm (see figure 3), with terminal massive ventricular extension.

Cerebral arteriosclerosis of all of the basilar vessels was described as marked in four of the cases and moderate in three. Of these seven cases, it should be noted that only three were instances of arteriosclerotic aneurysms whereas the remaining four showed the classical picture of "berry" aneurysm.
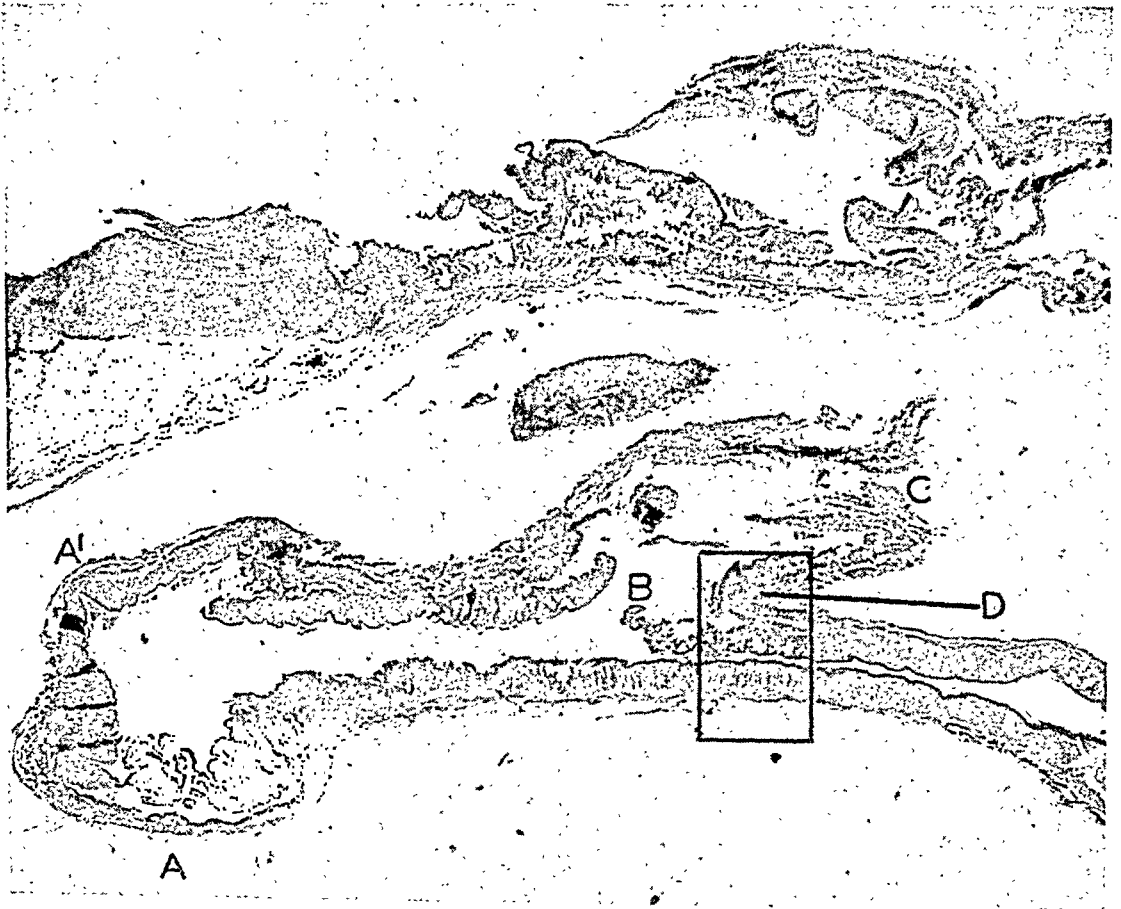
FIG. 5. *Case 3.* Longitudinal section of vertebral artery with multiple "berry" aneurysms, one showing site of rupture. A and A¹—unruptured aneurysms. B—neck of ruptured aneurysm. C—site of rupture. D—necrosis of arterial wall, enlarged in figure 6. Remnant of pia-arachnoid with subarachnoid hemorrhage at upper left margin. L. P. 48 mm.

Microscopic observations and discussion. Histological preparations of aneurysms were available in 25 of the 36 cases included in the series. All of the mycotic aneurysms were confirmed by section. The diagnosis of syphilitic aneurysm was established by the microscopic study, though the gross opinion was congenital aneurysm. It is our opinion that all aneurysms must be studied histologically to confirm the gross diagnosis in order to rule out complicating associated pathology of this type. Seven of the 12 ruptured "berry" aneurysms were studied in microscopic section. Hematoxylin and eosin stains were used routinely, with only an occasional elastic tissue stain. Defect of the media with loss of the muscle coat was commonly present in the "berry" group.

FIG. 6. *Case 3.* Higher magnification of insert in figure 5 through neck and wall of aneurysm showing necrosis and extensive acute inflammatory reaction at D (H. P. 8 mm.).

Certain facts stand out in this microscopic survey. Contrary to the original impression before initiating this study, there was found an unexpected degree of arteriosclerosis in the wall of the "berry" aneurysms. In the seven cases of this group in which sections were studied, five were under the age of 50. Case 2 was 12 years old and showed swelling and thickening of the elastic membrane. No other evidence of arteriosclerosis was present. Case 34, a 35 year old white woman, showed an inordinate degree of atheroma, thickening and hyalinosis of all coats and distortion of the vessel by eccentric thickening and thinning of the wall. It is significant that the remainder of the basilar vessels in this case were unusually free of atherosclerotic change. Cases 12 and 28 showed marked atherosclerosis and hyaline fibrosis of the wall, limited to the aneurysmal wall. The presence of such advanced local changes in the aneurysms precludes any definite statement as to the existence or absence of elastica within the aneurysmal sac. The absence of sclerotic changes in the basilar vessels outside of the aneurysm in the younger age group is of importance. Glynn demonstrated that weakening or rupture of the cerebral vessels failed to occur as long as the elastica remained intact. The disruption of the elastica in arteriosclerosis may offer one additional factor for explanation of rupture of the "berry" aneurysms. Schmidt[7] emphasized this point in the following statement: "In others of my cases, the wall of the aneurysm has shown obviously arteriosclerotic changes, while the rest of the cerebral vessels did not reveal any sign of arteriosclerosis on microscopic examination." Strauss et al.[8] also stressed the finding of focal arteriosclerotic changes in the "region of the aneurysms."

Case 3 is of particular interest. The finding of an extensive zone of necrosis within the wall of the vessel at the neck of the aneurysm with an acute inflammatory reaction (figures 5 and 6) suggests the mechanism of rupture. The reaction seems out of proportion to the degree of vital reaction which might be expected to follow upon spontaneous mechanical rupture of the vessel wall. This finding intimates some other unknown etiological factor in the production of the necrosis in the vessel wall with subsequent rupture. Although the finding of the non-specific necrosis in this case is an isolated one in the series, it presents a morphological demonstration of that additional mechanism thought necessary for rupture suggested by Richardson and Hyland.

In the two syphilitic cases, gummatous necrotic destruction of the wall accounted for the rupture in a similar fashion. A similar zone of necrosis was found in the wall of the internal carotid artery at the site of a traumatic arteriovenous aneurysm (case 10). In the mycotic group, necrosis of the vessel wall including the elastica, was verified in all cases as the cause of the aneurysm and the rupture (figure 9).

It is possible that some of the arteriosclerotic aneurysms found in the older age groups might represent sclerotic changes in preëxisting "berry"

FIG. 7. (*Above*) *Case 4.* Base of brain stem and cerebellum showing fusiform arterio-sclerotic aneurysm of basilar artery and extensive subarachnoid hemorrhage.
FIG. 8. (*Below*) *Case 5.* Coronal section of cerebrum showing large saccular arterio-sclerotic aneurysm of right middle cerebral artery deeply embedded in temporal lobe.

FIG. 9. *Case 6.* Mycotic aneurysm of small leptomeningeal vessel in a case of cavernous sinus thrombosis showing intact vessel wall below, and necrosis and marked acute inflammation above (H. P. 8 mm.).

Fig. 10. *Case 7.* Gummatous lesion of wall of ruptured aneurysm of left internal carotid artery and adjacent pia-arachnoid in a case of active meningo-vascular syphilis (L. P. 16 mm.).

aneurysms. In this paper, such instances are listed as arteriosclerotic if marked arteriosclerosis of the cerebral vessels was present. The saccular aneurysm seen in case 5 (figure 8) and the fusiform sac seen in case 4 (figure 7) probably do represent true arteriosclerotic aneurysms because of their location and size.

It is of interest and worthy of reiteration that once the aneurysmal pouch is formed, local vascular disease in the form of atheroma, sclerosis or actual necrosis seems to predominate in the defective part of the vessel.

SUMMARY AND CONCLUSIONS

1. Thirty-six cases of intracranial aneurysms of the cerebral arteries are presented.

2. Forty-two aneurysms are included, subdivided as follows: "berry" 22, mycotic 11, arteriosclerotic 6, syphilitic 2, traumatic (arterio-venous) 1.

3. The presence of arteriosclerosis and of necrosis in the wall of the aneurysm is stressed in the mechanism of rupture.

4. On the basis of the recorded observations, careful histological study of all ruptured and unruptured aneurysms for evidence of atherosclerosis, for active degeneration and necrosis, and for evidence of specific and non-specific inflammation, is indicated for the further elucidation of this problem.

BIBLIOGRAPHY

1. RICHARDSON, J. C., and HYLAND, H. H.: Intracranial aneurysms; clinical and pathological study of subarachnoid and intracerebral hemorrhage caused by berry aneurysms, Medicine, 1941, xx, 1–83.
2. FORBUS, W. D.: On the origin of miliary aneurysms of the superficial cerebral arteries, Bull. Johns Hopkins Hosp., 1930, xlvii, 239.
3. GLYNN, L. E.: Medial defects in the Circle of Willis and their relation to aneurysm formation, Jr. Path. and Bact., 1940, li, 213.
4. MARTLAND, H. S.: Spontaneous subarachnoid hemorrhage and congenital "berry" aneurysms of the Circle of Willis, Am. Jr. Surg., 1939, xliii, 10.
5. DIAL, D. L., and MAURER, G. B.: Intracranial aneurysms; report of thirteen cases, Am. Jr. Surg., 1937, xxxv, 2.
6. O'CROWLEY, C. R., and MARTLAND, H. S.: The association of polycystic disease of the kidneys with congenital aneurysms of the cerebral arteries, Am. Jr. Surg., 1939, xliii, 3.
7. SCHMIDT, M.: Intracranial aneurysms, Brain, 1930–1931, liii, 489.
8. STRAUSS, I., GLOBUS, J. H., and GINSBURG, S. W.: Spontaneous subarachnoid hemorrhage; its relation to aneurysms of cerebral blood vessels, Arch. Neurol. and Psychiat., 1932, xxvii, 1080.
9. McDONALD, C. A., and KORB, M.: Intracranial aneurysms, Arch. Neurol. and Psychiat., 1939, xlii, 298–328.

THE DIAGNOSTIC QRS PATTERNS IN MYOCARDIAL INFARCTION *

By M. M. Hurwitz, R. Langendorf, and L. N. Katz, F.A.C.P.,
Chicago, Illinois

In the electrocardiographic diagnosis of recent myocardial infarction, so much emphasis has been placed on the S–T–T configuration, because of the diagnostic value of its evolution, that the importance of the QRS pattern has been insufficiently stressed. Recent experience has shown that several conditions such as acute diffuse pericarditis,[1] acute cor pulmonale,[2] acute nephritis,[3] toxemias of pregnancy,[4] hyperthyroid state in flux,[5] etc., may sometimes closely imitate the S–T–T pattern of myocardial infarction and less closely its evolution, without showing the specific QRS patterns expected in myocardial infarction. It therefore seemed desirable to investigate the QRS patterns encountered in recent myocardial infarction in greater detail, with the thought in mind that such knowledge would increase the ability to use the electrocardiogram in differential diagnosis. Although some studies on QRS patterns in myocardial infarction have appeared in the past,[6] they have been incomplete for the most part.

The present study is based on an analysis of serial records in 369 cases selected from the files of the Heart Station covering the past six years. In obtaining these data some 800 series of records classed in the files as indicative of myocardial infarction were examined. All cases in which there was the slightest doubt as to the electrocardiographic diagnosis were discarded, even when, as was true in many instances, the clinical picture was unequivocal. We doubtless discarded many cases of recent myocardial infarction in this way. However, since we were interested in establishing the electrocardiographic patterns characteristic of myocardial infarction, the non-characteristic changes in cases known to have recent myocardial infarction clinically would not be of value in utilizing the electrocardiogram as an independent objective diagnostic procedure. It is noteworthy that of the 369 cases of this series in 36 in which necropsies were available the diagnosis of the presence and location of the infarct was confirmed. All 369 cases in this study had chest leads; approximately 75 per cent had both chest leads CF_2 and CF_4, the remaining 25 per cent having only chest lead CF_2. Most of the cases had long series of records, some with controls before, and more with records after stabilization had been completed. In a few instances, cases with single records were included, but only when they were absolutely typical. The use of serial records and chest leads, as emphasized before, is of considerable

aid in diagnosing recent myocardial infarction, and reliance on single limb lead records, except in unusual circumstances, may be misleading.

The distribution of the cases into types based on both the S–T–T and QRS patterns is shown in table 1. The most significant analysis revealed in this study was the limb lead QRS patterns in anterior wall infarction; but, before presenting this, our findings in the other patterns merit brief comment.

TABLE I

Distribution of the 369 Cases of the Series into Types Based on the
S-T-T and QRS Configuration

Pattern	No. of Cases	% of Cases
Anterior wall	190	51
Posterior wall	141	38
Combined anterior and posterior wall	20	6
Atypical	18	5
Totals	369 cases	100%

It was noted, incidentally, that T-wave inversions occurring at some time during the evolution in all three limb leads (T_N type) [7] were found in 41 of the 369 cases (11 per cent). This was more frequent in the combined and atypical infarct pattern groups (45 per cent and 28 per cent respectively) than in the anterior or posterior wall patterns (7 per cent and 9 per cent respectively). This compares reasonably with a previous report,[7a] and the greater frequency of the T_N type in combined anterior and posterior wall patterns substantiates the concept that the T_N is evidence of a more widely distributed area of infarction.

Evidence of acute diffuse pericarditis complicating recent infarction [8] was diagnosed in the electrocardiogram in 13 cases, nine with anterior (5 per cent) and four with the posterior wall patterns (3 per cent). The diagnosis was made only in cases of these two infarct patterns when S–T was elevated in all three limb leads for a time, or when marked S–T elevation occurred in two limb leads and the S–T segment was not depressed in the third limb lead. Obviously, this diagnosis was not attempted in instances of atypical or combined infarct patterns.

The 18 cases classed as atypical infarct patterns (table 1) did not fall into the patterns of anterior, posterior, or combined infarcts, but represent true instances of myocardial infarction, as their S–T–T evolution was characteristic in showing waxing and waning of the T waves and restoration of the deviated S–T segments toward normal. They may represent examples of small atypically located infarcts, but no autopsy findings were available. Obviously an analysis of their QRS patterns in our present state of knowledge would not be of much value and was therefore not attempted.

In 20 cases patterns were encountered having some characteristics of anterior and others of posterior wall infarction. In two of these post-mortem findings revealed the presence of infarction in both localities; in one

both were recent, in the second the two were of different ages. It is probable that some of these 20 cases represent recent infarction in one locality superimposed on an old infarct in the other, whereas others represent simultaneously occurring infarcts in both areas. It is also possible that large lateral wall infarcts extending to both regions may account for some of these cases. The diagnosis was made in this group on the configuration of the QRS as well as that of the S–T–T in both the limb and chest leads. When the dominant pattern in the limb and the dominant one in the chest leads were analyzed, it was found that in 15 of the cases (75 per cent) the limb leads had a predominantly posterior wall pattern while the chest leads had a predominantly anterior wall pattern. In only one case was the reverse true. In the remaining four it was not possible to speak of a dominant pattern in either the chest or limb leads, the admixture being equally distributed between anterior and posterior wall characteristics. Knowledge of the QRS patterns encountered in anterior and posterior wall infarction was useful in this classification, and their evaluation is therefore valuable in recognizing atypical and combined types of infarction contours.

POSTERIOR WALL PATTERNS

There were 141 cases showing patterns indicative of posterior wall infarction. In four of these, two types of limb lead QRS patterns were found in the serial records of the cases, making a total of 145 limb lead QRS patterns for analysis. The distribution of these limb lead QRS patterns is

TABLE II

Frequency of Various Types of QRS Patterns in the Limb Leads Encountered
in Posterior Wall Infarction

Pattern	No. of Cases	% of Cases
Diphasic QRS with deep Q waves in Leads II and III	61	42
Triphasic QRS with deep Q waves in Leads II and III	3	2
Triphasic QRS_2 and diphasic QRS_3 with deep Q waves	2	1
Diphasic QRS_2 with deep Q and QRS_3 entirely inverted	13	9
Triphasic QRS_2 with deep Q and QRS_3 entirely inverted	17	12
Triphasic QRS_2 with deep Q and M-shaped QRS_3	1	$\frac{1}{2}$
QRS entirely inverted in Leads II and III	7	5
Diphasic QRS_3 with deep Q and QRS_2 normal	26	18
Triphasic QRS_3 with deep Q and QRS_2 normal	1	$\frac{1}{2}$
All other cases not falling into any of above categories	14	10
Totals	145	100
Low "voltage"	20 cases	14%
Intraventricular block	12 cases	9%

shown in table 2. It will be seen that in 89 of the 145 instances (61 per cent) a diphasic QRS_3 with a Q wave 25 per cent or more of the upright phase (the so-called diphasic Q_3 pattern) was present (figure 1); in 61 of these a similar diphasic Q pattern occurred in Lead II. Further examination revealed that in all except 14 of the 145 cases equivalents of the diphasic Q

pattern were present in Lead II, Lead III, or both (table 2). These equivalents consisted of (a) a triphasic W-shaped QRS with a first inverted phase 25 per cent or more of the upright phase, the so-called triphasic Q_2 and Q_3 patterns (figure 1), and (b) entirely inverted QRS_3 with diphasic or tri-
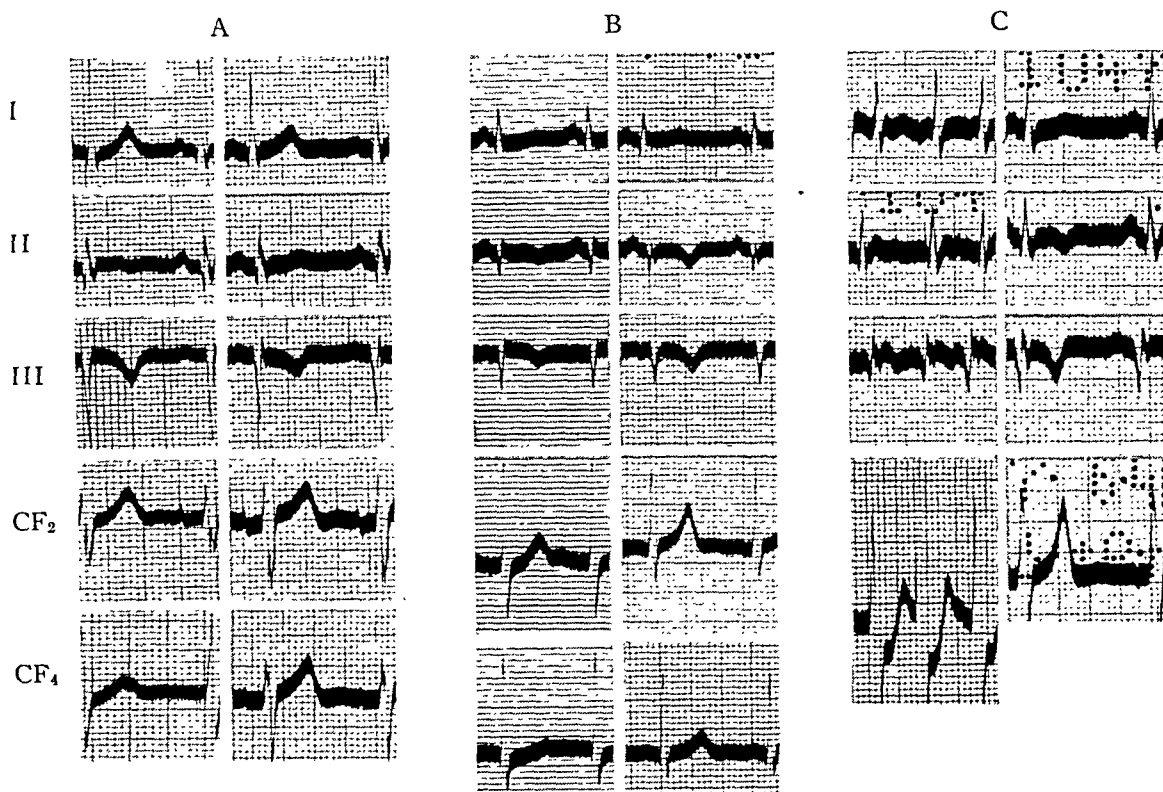
Fig. 1. Three cases of posterior wall infarction to illustrate the diphasic Q type of QRS in Leads II and III and its variants, the triphasic W-shaped QRS and the entirely inverted QRS. The latter in Lead III has the same significance as a Q type only when QRS_2 is of the diphasic or triphasic Q type. Discussed in text.

A. An example of a triphasic QRS_2 of the Q type and QRS_3 entirely inverted (in the first record), the latter subsequently changing to a diphasic Q type (in the second record). The two records were taken a year apart in a case with a recent myocardial infarction developing five days before the first record.

B. An example of a diphasic Q type of QRS_2 (in the first record), becoming a triphasic W-shaped QRS (in the second record) and a diphasic Q type of QRS_3 becoming an entirely inverted complex. The two records were taken 15 days apart in a case with a recent myocardial infarction developing one day before the first record.

C. An example of a diphasic Q type of QRS_3 (in the first record) becoming a triphasic Q type (in the second record). Note the auricular fibrillation present in the first record. The two records were taken five weeks apart in a case with a recent myocardial infarction developing six days before the first record.

phasic Q patterns in Lead II or QRS_2 inversion. The correctness of the interpretation that these are diphasic Q equivalents was shown by their serial evolution from or into the more typical patterns (figure 1). Although the diagnosis could almost always be made from the S–T–T pattern and its evolution, the fact that the Q pattern may remain when the S–T–T has lost its characteristics makes the diphasic Q pattern or its equivalent significant

not only in the diagnosis of recent infarction but also in indicating the presence of an old infarct, particularly when QRS_2 as well as QRS_3 shows the Q pattern or its equivalent (figure 1 A). It has been our custom in these cases, therefore, not to consider inverted QRS_3, or QRS_2 and QRS_3, as being indicative of left ventricular preponderance in the absence of deep S waves, the QRS inversion being ascribed to the recent or old infarct per se. Conditions other than infarction, notably obesity and right ventricular hypertrophy, may show a Q_3 pattern, but in such cases no Q_2 pattern is found.

The chest lead changes were not as significant in the diagnosis of posterior wall infarction as in the anterior wall type, but often aided considerably in showing depressed S–T segments in the acute stage and waxing T waves in the healing stage of infarction (figure 1 C). In only two instances were the chest leads characteristic of infarction in the presence of noncharacteristic limb lead changes, this being in sharp contrast to the anterior wall type in which 9 per cent of our cases showed pathognomonic chest lead changes in association with non-specific limb lead abnormalities. In most cases, however, the chest lead QRS was of normal configuration (being, of course, prolonged in the 12 cases with intraventricular block, and occasionally showing low "voltage" when the limb leads did also). In only 13 cases was QRS in CF_2 mainly upright with a small final phase (less than five mm.) which is abnormal [9] (figure 1 B).

In 10 cases autopsy studies were available and the expected infarction was found in all.

The appearance of a deep S wave in Lead I as a concomitant finding with a Q_3 pattern (figure 1 C) was found in only 17 cases and is, therefore, statistically not of great significance. Nevertheless, its occasional occurrence in posterior wall infarction is of moment since failure to appreciate this may lead to attributing it to some other cause. The S_1 and Q_3 combination is much more significant in the diagnosis of pulmonary embolism and is almost pathognomonic when associated with the characteristic S–T–T changes of this state.

ANTERIOR WALL PATTERNS

Unlike posterior wall infarction, the presence of a Q pattern is not so common in anterior wall infarction. In this series, a QRS_1 with a deep Q wave was encountered in only 54 of the 190 cases (28 per cent), in 37 instances the QRS_1 being diphasic and in 17 the triphasic W-shaped equivalent (figure 7 B). Just as in the posterior wall infarction pattern, so also in the anterior, the entirely inverted QRS_1 with (figure 7 B) or without (figure 7 D) notching on its downstroke was found, but here in only eight instances. In nine cases a Q_2 pattern or its equivalent as well as a Q_1 pattern was found.

It is obvious that reliance only on the presence of the pathognomonic Q_1, or Q_1 and Q_2 patterns, was helpful in only a little over 25 per cent of the cases. Reliance must therefore be placed on other characteristics of the QRS if its contour in the limb leads is to be of value. The series of 190

cases of anterior wall infarction was, therefore, reëxamined for other patterns which might be of diagnostic significance. In this analysis the cases with Q_1, or Q_1 and Q_2 patterns, were lumped together with those not showing them; cases with low "voltage" and intraventricular block (QRS duration 0.12 second or more) were not excluded.

This breakdown showed five distinct limb lead QRS patterns besides a miscellaneous group. In table 3 are shown the characteristics and frequency

TABLE III

Description and Frequency of the Various Types of QRS Patterns in the Limb Leads Encountered in 194 Combinations in 190 Cases of Anterior Wall Infarction Patterns ·

Type	Description	No. of Cases	% of Series	No. Cases with Low "Voltage"	No. Cases with Q_1 Pattern*	No. Cases with Intraventricular Block†
I	QRS_1 relatively small and upright, QRS_2 and QRS_3 diphasic and mainly or almost entirely inverted with deep S waves which are larger than QRS_1	35	18	2	19	13
II	QRS_2 and QRS_3 similar to type I, but QRS_1 upright and relatively normal in size	28	14	4	5	4
III	QRS_1 relatively small and upright, QRS_2 and QRS_3 entirely or mainly upright	15	8	2	7	0
IV	QRS_1 small and equiphasic, or mainly or entirely inverted; QRS_3 mainly or entirely upright; QRS_2 upright, equiphasic, or inverted	14	7	3	7	0
V	QRS mainly or entirely inverted in all three limb leads	4	2	3	1	1
All other cases not falling into any of the above groups		98	51	17	15	13
Totals: No. of cases		194		31	54	31
% of entire series			100%	16%	27%	16%

* Described in text.
† QRS in limb leads 0.12 sec. or more.

of each, as well as the number of instances with Q_1 patterns, with low "voltage," and with intraventricular block. In 186 of the cases only one QRS type was found in the serial curves, but in four, two patterns were revealed, making a total of 194 patterns in the 190 cases.

As table 3 will show, the relatively small QRS_1 is the common attribute in types I and III and constitutes the abnormality in 50 cases. When to these are added the instances of small equiphasic or inverted QRS_1 common to types IV and V, which are the other varieties of abnormal QRS_1 en-

countered in anterior wall infarction, 68 of the 194 patterns are accounted for, a larger group than showed the Q_1 types. Relatively small and upright, small and equiphasic, or inverted QRS_1 are, therefore, more common concomitants of anterior wall infarction than the Q_1 pattern.

A   B
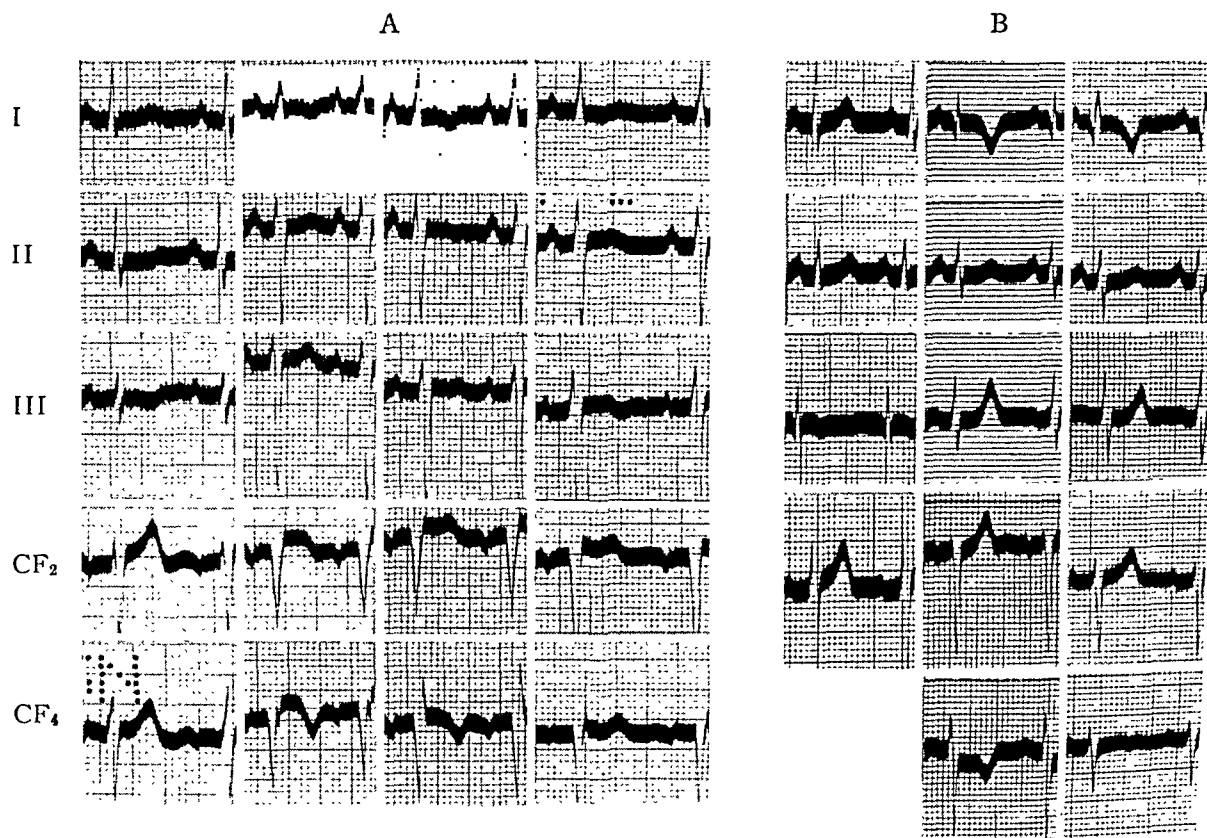
FIG. 2. Two cases of anterior wall infarction showing the development of type I QRS pattern after infarction, viz., small QRS_1 and deep S waves in Leads II and III. Discussed in text.

A. The series shows a control record before infarction, and records taken three weeks, two months, and eight months after a recent myocardial infarction. Note, in addition to the type I QRS pattern, the absence of a Q_1 pattern and the typical chest lead changes, including the diphasic Q pattern in CF_4 in the third and fourth records. The last record showing the QRS residue of the anterior infarction would be difficult to distinguish from left ventricular preponderance except for QRS in CF_4.

B. The series shows a control record before infarction and records taken the same day and three weeks after a recent myocardial infarction. Note, in addition to the type I QRS pattern, the Q_1 pattern and the non-characteristic QRS in the chest leads.

It is further significant that S_2 and S_3 occurred more frequently than the Q_1 type, viz., in 63 out of 194 patterns (types I and II of table 3). Furthermore, as table 3 shows, the S_2 and S_3 occur in the absence of the Q_1 types and, in type II, in the absence of small QRS_1. Thus it would appear that the S_2 and S_3 type is a more common concomitant of anterior wall infarction than the Q_1 type or the low and upright, low and equiphasic, or inverted QRS_1 contours; in fact, the number of cases showing S_2 and S_3 were equal to ¾ of the cases showing Q_1 types and/or low and upright, low and equiphasic, or inverted QRS_1, viz., 63 as against 88 cases respectively. In fact, in 21 cases

(in type II) the S_2 and S_3 were the only QRS pattern abnormalities, the QRS_1 being entirely normal.

A. Type I QRS of Anterior Wall Infarction. This type was first recognized as of diagnostic significance by Wilson et al.[65] and by Winternitz[61] and has recently been stressed again.[10] Our study reveals it to be the most significant single variety since it combines the two common characteristics of anterior wall infarction, relatively small QRS_1 and deep S_2 and S_3 (figures 2, 3 and 5). Therefore, it merits consideration at some length.

The first question that arose was the extent to which this QRS pattern was attributable to the infarct. In six of the 35 cases in this group control records before the infarction occurred were available. In four of these the S-wave patterns were present in Leads II and III in the control records, being therefore attributable to preëxisting left ventricular preponderance. In these four cases, two showed deepening of the S waves after infarction (figure 2, A), and two did not, but in all four QRS_1, which was of normal size in the control records, decreased noticeably after the infarction. A like decrease in QRS_1 also occurred in the two other cases which had no S_2 and S_3 in the control records at the same time that the S_2 and S_3 appeared (figure 2, B). Thus it would seem that while preëxisting left ventricular preponderance may be responsible for the S_2 and S_3 in the type I QRS pattern after anterior wall infarction, this pattern can develop in some cases in the absence of left ventricular hypertrophy as a result of the infarct per se (figure 2, B). This latter view is supported by the fact that while 10 out of the 12 autopsied cases with this pattern showed left heart enlargement and hypertrophy as well as the anterior wall infarct, two others showed the infarct without any cardiac enlargement. It is, therefore, not justifiable to diagnose left ventricular hypertrophy when a type I QRS pattern is encountered in anterior wall infarction since the infarct itself may be the sole cause of the pattern.

This deduction is especially significant in the stage of stabilization of the record or later when the records have undergone restitution. At these times the S-T-T pattern may no longer be characteristic and the diagnosis of left ventricular preponderance alone might be entertained (figure 3). Six of the 35 cases fell into this category. In five of these cases the stabilized records resembled the mixed type of left ventricular preponderance[11] * in that with the deep S-waves in Leads II and III indicative of the first type, the S-T-T Lead I was indicative of the second type of left ventricular preponderance, viz., S-T was depressed and bowed upward and T was inverted and asymmetrical. While in all five QRS_1 had increased somewhat in size, in three it was sufficiently small still to fit the description of type I QRS of anterior wall infarction (figure 2, A). In the other two it was suf-

---

* In type I of left ventricular preponderance deep S-waves are present in Leads II and III. In type 2, a deep S_3 is present while $S-T_1$ is depressed, bowed upward, and T_1 is inverted or diphasic. In the mixed type, the characteristics of both the first and the second types are present. In all three types QRS_1 is tall.[9]

ficiently large to make the entire limb lead pattern indistinguishable from the classical mixed pattern of left ventricular preponderance (figure 3, B). The sixth case with complete restitution showed no abnormalities of the S–T–T at this time, and resembled the first type of left ventricular preponderance
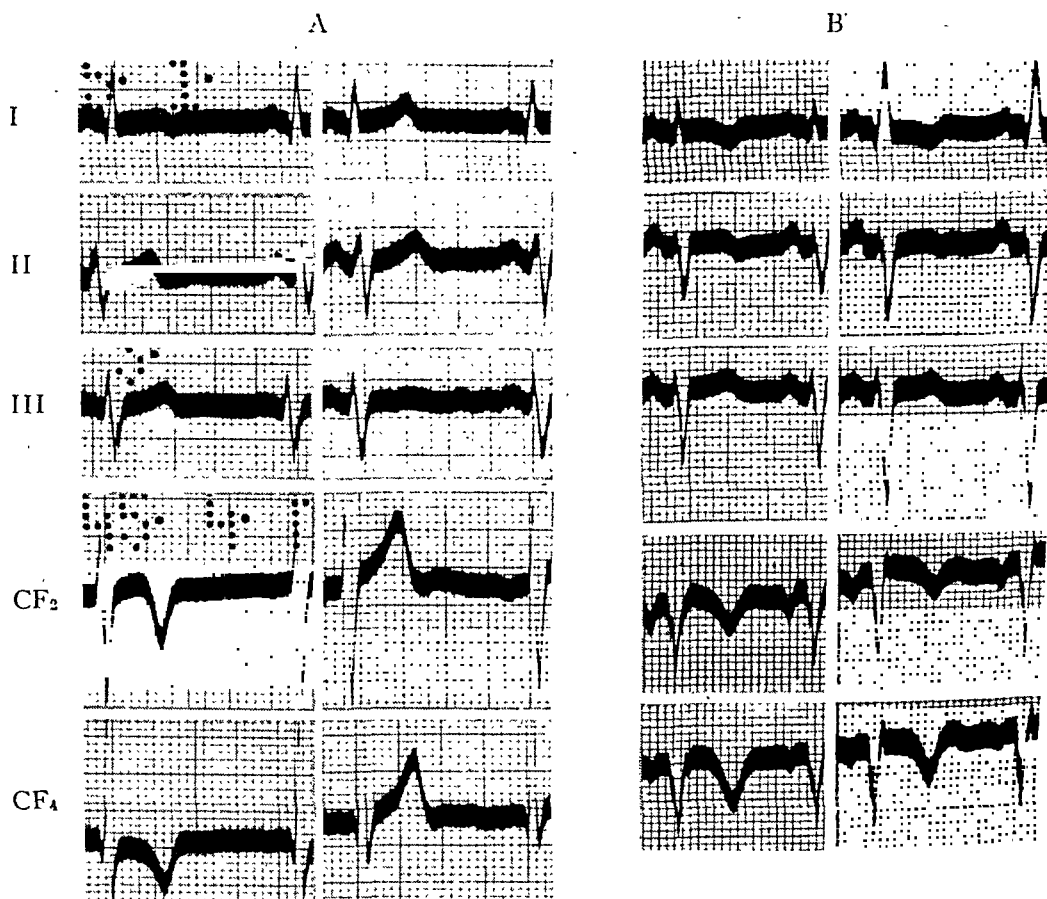
FIG. 3. Two cases of anterior wall infarction showing the type I QRS pattern, persisting in one (A) and changing to the type II in the other (B) after the record had stabilized. Discussed in text.

A. The two records were taken 14 months apart. The first was taken some time during the healing stage of the infarction. Note the atypical QRS patterns in the chest leads. In the second record only the type I QRS pattern (plus Q_1) remains as the residue of the infarction.

B. The two records were taken 11 months apart, the first being taken several weeks after the infarct developed. Note the persistence of the T-wave inversion in the chest leads and the persistence of the Q type QRS in these leads associated with the type II QRS pattern in the limb leads as the residue of the infarction. The S–T–T configuration in the limb leads suggests left ventricular preponderance.

except for the relatively small QRS_1 (figure 3, A). In five of these six cases the QRST pattern in the chest leads (CF_2 and CF_4) was of the type that we have come to recognize as characteristic of a recent or as the residue of an old anterior wall infarct [9] so that the true nature of the limb lead QRS changes was indicated (figures 2, A and 3, B). In the sixth case the chest lead QRS pattern was normal in the entire series of records and the S–T–T

had returned to normal (figure 3, A). This case, therefore, would be difficult to diagnose once the records were stabilized.

The foregoing analysis indicates clearly that the QRS pattern in which deep S_2 and S_3 are present in diphasic QRS complexes in association with a
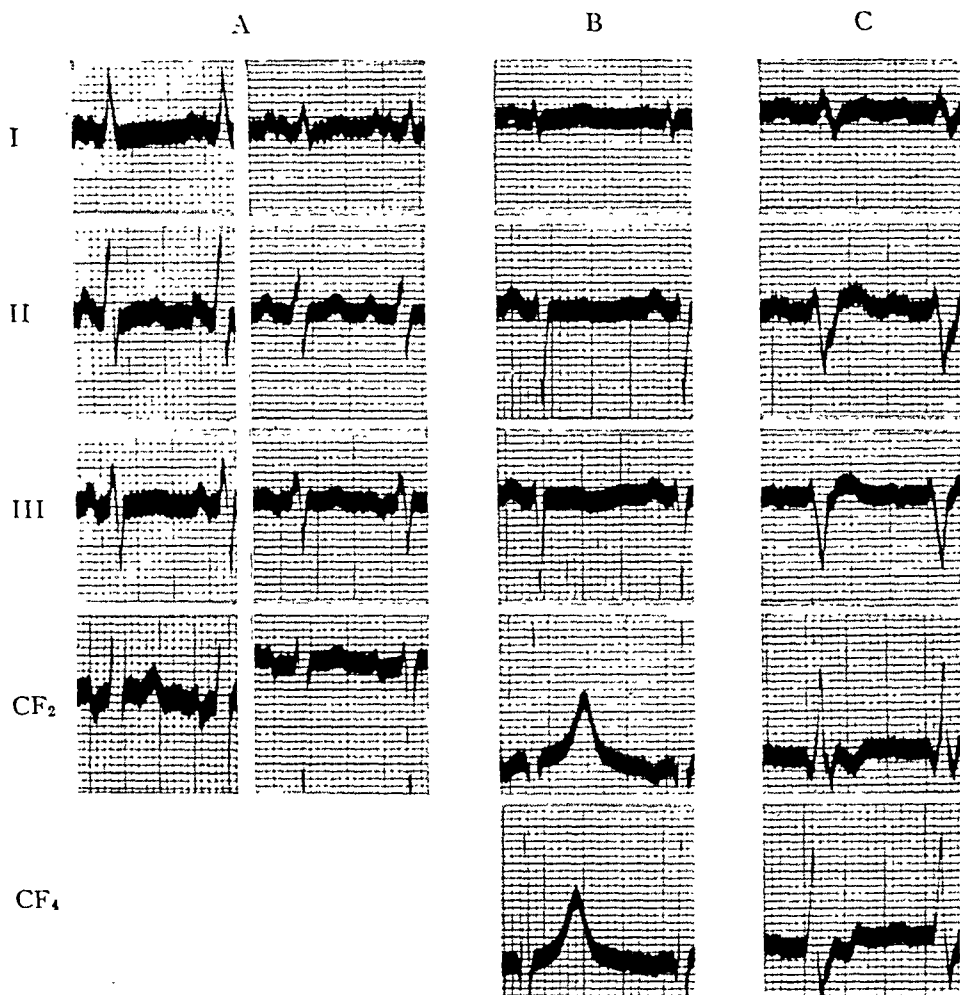
FIG. 4. Three autopsied cases with QRS patterns resembling the type I of anterior wall infarction but due to other conditions. In these cases there is an absence of findings indicative of infarction in the chest leads and QRS_1 is of the S type. Discussed in text.

A is a case of multiple valvulitis (rheumatic) leading to bilateral ventricular hypertrophy. Note the broad notched P waves in Lead I. The two records were taken 11 days apart.

B is a case of bilateral ventricular hypertrophy with marked emphysema to account for the right heart strain. There was nothing in the clinical story or autopsy protocol to explain the strain on the left heart.

C is a case of severe coronary sclerosis and myocardial fibrosis and the resulting bilateral ventricular hypertrophy. No evidence of myocardial infarction (old or recent) was seen. Note that the electrocardiogram shows evidence of intraventricular block (QRS longer than 0.12 sec.).

relatively small QRS in Lead I (smaller than either S_2 or S_3) may be the residue of an anterior wall infarction whether left ventricular hypertrophy is present or not. Furthermore, while the QRST pattern in the chest leads

may remain characteristic of the old anterior wall infarction, occasionally even this is absent.

1. *Other Causes for the QRS Pattern Resembling Type I QRS of Anterior Wall Infarction and Their Differentiation.* In order to determine under what other circumstances a QRS pattern in the limb leads resembling this type occurred, a survey was made for serial curves in our files showing this pattern (figure 4). Eleven cases selected at random were found in which this pattern occurred without S–T–T changes pointing to anterior wall infarction and in which the clinical history and findings or the autopsy showed the absence of infarction.

Seven of these 11 cases had necropsies and six of these showed evidence of combined left and right ventricular strain leading to measurable hypertrophy of both ventricles. The cause of the combined left and right strain was due in two instances to old rheumatic heart disease with multiple valvulitis (in one there was involvement of the aortic, mitral, and tricuspid valves and in the other, involvement of the latter two valves) (figure 4, A). In two other instances there was chronic cor pulmonale associated with emphysema, both of these patients having had bronchial asthma; the hypertrophy of the left ventricle in one of these was caused by systemic hypertension evident clinically, in the other, its cause could not be determined (figure 4, B). In all of the above four cases the coronary arteries were normal at necropsy. The only two of the seven autopsied cases showing intraventricular block revealed severe coronary artery disease and myocardial fibrosis, in addition to the hypertrophy of both ventricles (figure 4, C). No cause for the hypertrophy was revealed other than the severe coronary sclerosis and this was considered its cause.[12] The last of the seven autopsied cases showed moderate coronary sclerosis with moderate myocardial fibrosis and "brown atrophy" but no valvular deformities or measurable hypertrophy. The roentgenogram and autopsy both revealed a very low diaphragm and dropped heart, and the QRS pattern was explained on this basis (discussed below).

In three of the other four cases without autopsy, pulmonary emphysema was present, associated in one instance with mild hypertension and in the other two with evidence of marked arteriosclerotic heart disease. In the fourth case there was no clinical evidence of heart disease or any cardiac history, the records on this 44 year old patient being taken as a check before electric shock therapy for his mental state.

The differentiation of these cases from the type I QRS pattern of anterior wall infarction is not too difficult. Aside from the absence of the S–T–T changes characteristic of anterior wall infarction, none of these cases had a Q_1 type pattern whereas 19 of the 35 cases with infarction did. Furthermore, the chest lead QRST patterns were not indicative of either recent or old anterior wall infarction. The chest lead QRS patterns in four of these were within normal limits while the other six showed a QRS in lead CF_2 that was abnormal in being upright and W-shaped (figure 4, B and C) with an initial inverted phase less than 3 mm.; this was associated with the same type of

QRS in lead CF_4 (normal in this lead) in some (figure 4, B). In only two of the 11 cases was QRS in CF_2 mainly inverted, but here the first upright phase was more than two millimeters and thus fell within the normal range; in these two cases the QRS in lead CF_4 was normal, being upright and W-shaped. The eleventh case had no chest leads.

The cause of this peculiar QRS pattern in the absence of infarction appears to be due to combined heart strain, the change in QRS_1 being due to right ventricular strain, and the changes in QRS_2 and QRS_3 to left ventricular strain. It is significant that this pattern is seen relatively more frequently in cases of chronic cor pulmonale associated with left heart strain than in cases of combined heart strain due to rheumatic heart disease. This difference may be due in part to the change in the heart's position in association with the low diaphragm, viz., a more pendulous heart with rotation on its own long axis from right to left. Cases have been reported [13] in which this QRS pattern occurred with a low diaphragm and pendulous heart without clinical evidence of either right or left heart strain; this was present in one of our own cases. The cause of this QRS pattern, aside from anterior wall infarction, therefore, appears to be either combined heart strain (figure 4, A and B), a pendulous heart, or both in combination. In addition, this pattern occurring with intraventricular block as in two of our cases of combined strain (figure 4, C) may be due not only to the above causes, but possibly also to bilateral involvement of the bundle branch systems or to unilateral block in one of the bundle branch systems with muscular hypertrophy of the contralateral ventricle. The type I QRS pattern has also been described as a transitory change occurring in anginal attacks.[14]

Thus, there are a number of factors in addition to anterior wall infarction which give rise to this QRS pattern, but the occurrence of a relatively small QRS_1 and diphasic QRS with deep S waves in Leads II and III should always arouse suspicion of an anterior wall infarction, and this cause should be excluded before attributing it to other mechanisms. In this regard, the S–T–T pattern and evolution, the presence or absence of a Q_1 type pattern, and the QRST pattern of the chest leads are valuable adjuncts in the differentiation.

2. *Cause for the Type I QRS Pattern in Anterior Wall Infarction.* Obviously this QRS pattern may have existed before the infarction occurred and its cause would thus be the same as in cases without infarction. It could furthermore be due to infarction superimposed on a preëxisting left ventricular preponderance, several examples of which have been cited above (four out of six cases with control records), or on a preëxisting intraventricular block of which no examples could be found in our series, since none of the six cases with control records had intraventricular block before the infarction occurred.

A clue to another cause of this pattern is revealed by the great frequency of intraventricular block occurring in this type (figure 5), viz., 13 out of 35 cases (37 per cent) as compared with 18 out of 159 cases (11 per cent) in all other QRS patterns, or 31 out of all 194 patterns (16 per cent). The chest

lead QRS pattern in these 13 cases with intraventricular block is of the variety seen with intraventricular block of the broad S_1 pattern occurring with anterior wall infarction and attributable to involvement of the right bundle branch system.[16]   It would appear that block involving the right
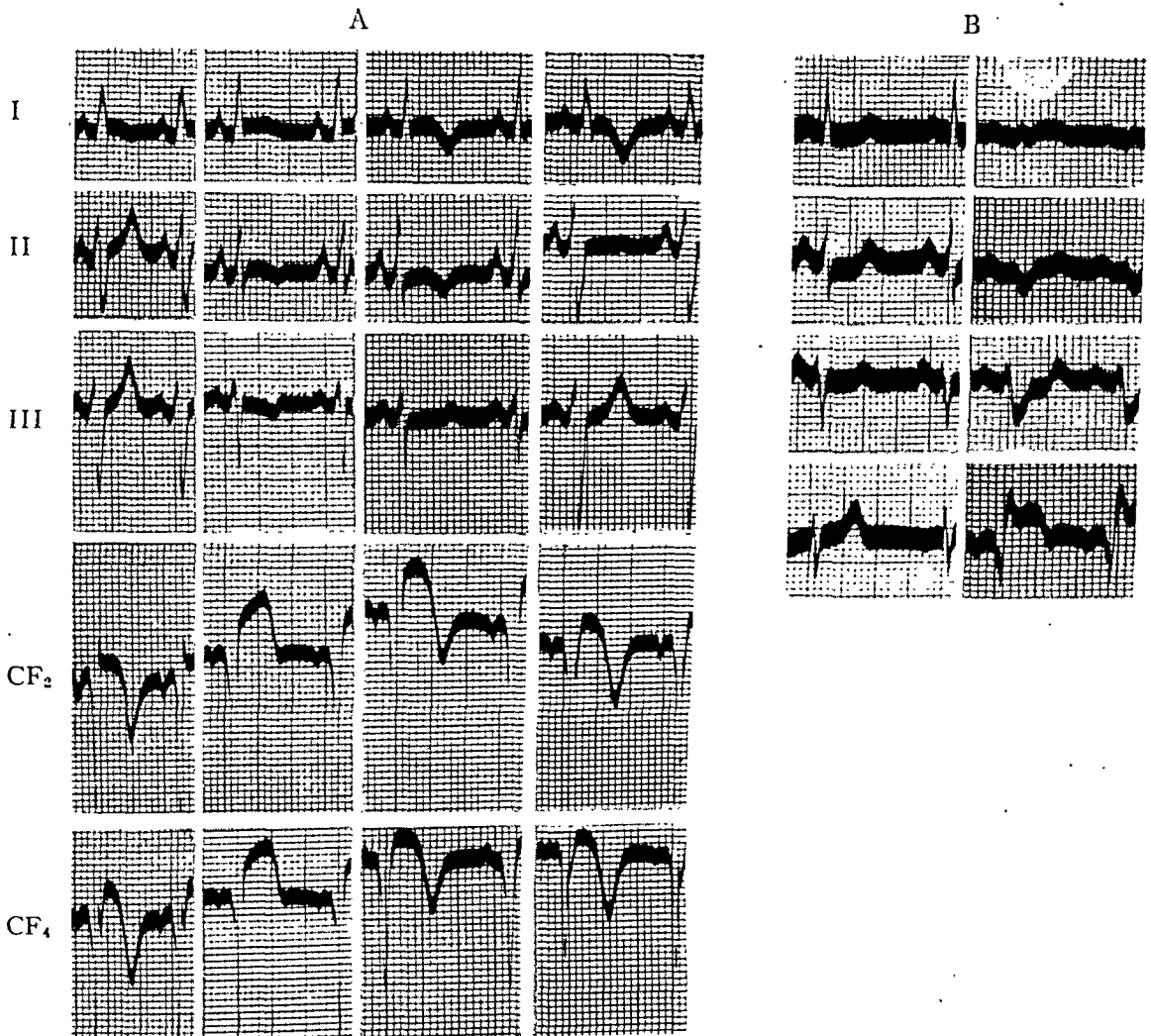
Fig. 5.   Two cases of anterior wall infarction to show the influence of intraventricular block in producing the type I QRS pattern.   Discussed in text.
    A. The series of records was taken 2, 5, 15 and 31 days after the development of in-farction.   This is an instance of intermittent intraventricular block; the block (with QRS longer than 0.11 second) present in the first and fourth records and absent in the second and third.   In this case, only when intraventricular block developed did the characteristic type I QRS pattern appear.   Note the characteristic chest leads.
    B. A control record and a record taken two days after the development of the in-farction.   After infarction, intraventricular block developed with a characteristic type I QRS pattern.   The chest lead CF_2 is also characteristic and shows the diphasic Q type pattern.

bundle branch system due to infarction of the septum as well as of the anterior wall was responsible for this combination.   In three of the cases with intraventricular block in which autopsy findings were available, such septal and anterior wall infarction was found, the septum being involved in

the region adjacent to the anterior wall. The relationship of this pattern to QRS prolongation is further shown by the fact that in five cases this pattern developed only when QRS lengthened to 0.10 second or more in duration, even though the electrocardiogram before this time had already assumed a characteristic coronary contour as evidenced by the S–T–T changes. Furthermore, in three of these five cases, this QRS pattern was only a transitory finding, disappearing when QRS again became shorter in duration (figure 5, A). Even in those cases not showing sufficient QRS prolongation to merit the diagnosis of intraventricular block, this type I QRS pattern may be due to extension of the infarct to the interventricular septum, as occurred in six of the nine autopsied cases showing a QRS of not more than 0.12 second in duration.

Thus it would appear that this QRS pattern in anterior wall infarction may be due to (*a*) causes giving rise to this pattern in the absence of infarction, (*b*) to the superimposition of an anterior wall infarction on a preexisting left ventricular preponderance, (*c*) to the superimposition of anterior wall infarction on preëxisting intraventricular block (of the right bundle branch system) from any cause, (*d*) to the simultaneous or successive involvement of the anterior wall and adjacent septum by the infarct, or (*e*) to infarction of the anterior wall alone.

3. *Prognostic Significance of the Type I QRS Pattern in Anterior Wall Infarction.* It was not possible to make a satisfactory follow-up on these cases of infarction so as to compile accurate mortality figures. We were, however, able to determine which had autopsies at the hospital. It is significant that 12 of the 35 cases of the type I QRS pattern (⅓) had necropsies, whereas only 12 of the remaining 155 cases (1/13) had necropsies. Thus, it appears that cases of anterior wall infarction showing the type I QRS pattern have a poorer life expectancy than those showing other patterns. Apparently they represent instances of more extensive infarction or the superimposition of infarction on an already severely damaged heart whatever its cause.

B. *Type II QRS Pattern of Anterior Wall Infarction.* Since both the decrease in size of QRS_1 and the development of deep S_2 and S_3 were demonstrated to occur after infarction in type I, it is obvious that either of the above changes might occur without the other.

In the type II series, 28 cases of infarction with diphasic QRS complexes in Leads II and III with deep S waves in both and without a small QRS_1 (figure 6) were found (type 2, table 3). In all of these, except when low "voltage" was present, QRS_1 was more than 5 mm. in height, and in none was the S_2 as large as the upright phase of QRS_1. It is noteworthy that none of these cases came to necropsy, indicating a better life expectancy than in the group with type I QRS pattern. In five of these there was a Q_1 pattern; in the other 23, the only change in the QRS pattern in the limb leads (excluding intraventricular block and low "voltage") was the presence of deep S_2

and S_3. The problem of differential diagnosis from left ventricular pre-
ponderance once the records became stabilized is more difficult than in the
cases of type I.

In three cases without control records, the S waves in Leads II and III
were seen to become deeper during the early evolution of the series. In four
cases out of five in which control records were available, the S waves were
seen to develop after the infarction occurred. In two of these, QRS was
upright in all three limb leads in the control records (figure 6, A); in the
third, there was a small S wave in Lead II and a definite O wave in Lead III
in the control; and in the fourth definite Q waves in Leads II and III were
present in the control record, the residue of an old posterior wall infarct.
In all of these, therefore, the S waves in Leads II and III were clearly due
to the anterior wall infarction alone. The case with the Q_2 and Q_3 pattern
in the control also developed intraventricular block after infarction occurred
(figure 6, C). The fifth case with a control record showed the first type of
left ventricular preponderance in the control, and after infarction occurred the
S_2 and S_3 became more pronounced.

It would appear, therefore, that whereas the type II QRS pattern of
anterior wall infarction may be evidence of a preexisting left ventricular pre-
ponderance or intraventricular block, it may, on the other hand, be the sole
QRS contour change, with or without intraventricular block, in some cases
of anterior wall infarction. It need not be associated with a Q_1 type and may
remain as the sole residue of an old anterior wall infarct (figure 6, B).
Therefore, cases showing as their sole abnormality deep S waves in Leads II
and III are not always indicative of left ventricular preponderance, but may,
on occasion, represent the only evidence of an old anterior wall infarction
in the absence of left ventricular strain or hypertrophy.

FIG. 6. Three cases of anterior wall infarction showing the development of the type II
QRS pattern after infarction, viz., S_2 and S_3 with S_2 *not* larger in amplitude than QRS_1.
Discussed in text.

A. The series shows a control record before infarction and records taken seven days,
nine days and one month after a recent myocardial infarction. Note the appearance of a
deep S_2 and S_3 without a decrease in amplitude of QRS_1 which, in the last record, makes the
curve resemble that of left ventricular preponderance. However, the chest leads are char-
acteristic and even in the last record would indicate the correct etiology of the QRS pattern
of the limb leads.

B. The series shows records taken one day, three days and five weeks after a recent
myocardial infarction. Note that while QRS_1 became smaller in the second and third records,
the S_2 that developed was not larger than the amplitude of QRS_1. The first record shows
the S–T–T changes in the limb leads seen in the earliest stage of infarction. The second
record is diagnostic including the S–T–T pattern although the chest leads are not except for
QRS in CF_2 (already present in the first record). The third record, taken a month later,
resembles the contour of left ventricular preponderance and there is nothing at this time to
point to infarction as its cause.

C. The first record taken 10 days after a recent myocardial infarction has a QRS pat-
tern of posterior wall infarction in the limb leads, while the S–T–T in the limb leads and both
QRS and S–T–T in the chest leads are typical of anterior wall infarction. The second
record was taken one year later, and in the interim there was a questionable history of an-
other infarction. This record shows intraventricular block (QRS longer than 0.12 second)
and with this block the type II QRS pattern of anterior wall infarction developed. While
QRS_1 is decreased in size it is still larger than the S_2 which distinguishes the type II from
the type I pattern.
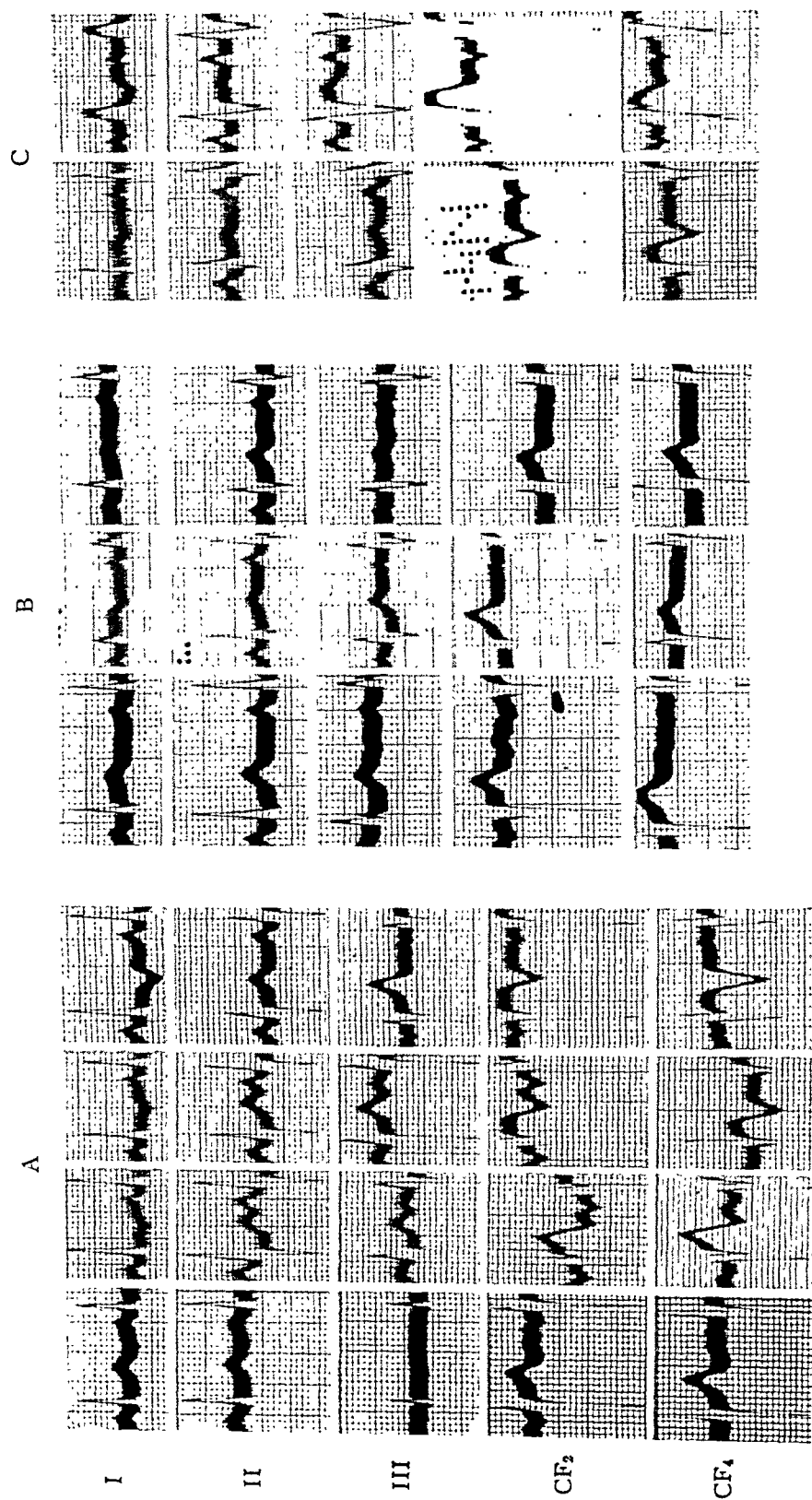
FIG. 6.

The presence of S_2 and S_3 in anterior wall infarction gives the mirror image of the Q_2 and Q_3 pattern seen so frequently in posterior wall infarction, and suggests that the diametrically opposite location of the infarcts gives rise to these mirror image changes. In addition to emphasizing changes in QRS_1 in anterior wall infarction, the occurrence of deep S_2 and S_3 deserves stress. The demonstrable occurrence of S_2 and S_3 alone in anterior wall infarction in the absence of left ventricular strain has led us to avoid the latter diagnosis in the presence of anterior wall infarction without other substantiating evidence for its presence.

C. Type III QRS Pattern of Anterior Wall Infarction. In this series 15 cases of small, mainly upright QRS_1 without deep S_2 and S_3 were found (type III, table 3), showing that this may be the sole limb lead QRS change in anterior wall infarction. In almost one-half of these (seven cases) a Q_1 pattern was encountered.

Whereas the small QRS_1 may be the result of a preexisting right axis shift, as was true in one case with a control record showing a small QRS_1 with a noticeable S wave, the small QRS_1 is usually the result of the infarction per se. In three of the cases with control records the electrocardiogram showed no QRS abnormalities in the controls, and the QRS_1 was seen to decrease in size from 12 to 3, from 9 to 3, and from 5 to 1 mm. respectively.

The diagnosis in three of the 15 cases was confirmed at necropsy, and no cardiac enlargement or noticeable displacement was found, the infarcts being the only abnormalities and being extensive in all, involving also the adjacent septum in two instances. Small upright QRS_1 may persist for some time,

FIG. 7. Four cases of anterior wall infarction showing the development of the type III QRS pattern after infarction in one (A), viz., QRS_1 small without S_2 or S_3 appearing; and of the type IV QRS pattern after infarction in three (B, C and D). viz., QRS_1 becoming mainly or entirely inverted with QRS_3 upright. Discussed in text.

A. The two records were taken, respectively, during the healing stage and about 18 months after a recent myocardial infarction. At the time of the second record the type III QRS pattern had disappeared although the chest leads and the small inverted T_1 were the residue of the infarction. The first record shows the typical maximal T stage, a characteristic QRS in CF_2, and in the limb leads a tiny QRS_1, the type III QRS pattern.

B. The three records were taken one, three and 11 days after the development of infarction. In the first record a small QRS_1 with a Q_1 is the only QRS abnormality in the limb leads making it a type III QRS pattern. In the other two records QRS_1 becomes inverted which, with QRS_2 and QRS_3 upright, makes this a type IV QRS pattern. In the second record QRS_1 is the triphasic W-shaped equivalent of the diphasic Q pattern, and in the third record the QRS_1 is inverted and notched, also an equivalent of the diphasic Q pattern. These characteristics of QRS_1 distinguish it from the inverted QRS_1 seen in right ventricular preponderance and aside from this, the S–T–T pattern and evolution, and the QRS in the chest leads are characteristic of the anterior wall pattern.

C. This record taken during the healing stage of a recent myocardial infarction shows a type IV QRS pattern. While the infarct is responsible for the QRS in the chest leads and the S–T–T configuration, in both limb and chest leads, the presence of deep S waves in Leads I and II as well as the presence of P-pulmonale suggests that the pattern in this record is the result of anterior infarction superimposed on a preexisting right ventricular preponderance.

D. The first record is a control taken before infarction, and the second was taken 11 days after the development of infarction. In the second record, QRS_1 becomes entirely inverted, the equivalent of the diphasic Q pattern, making this a type IV QRS pattern.
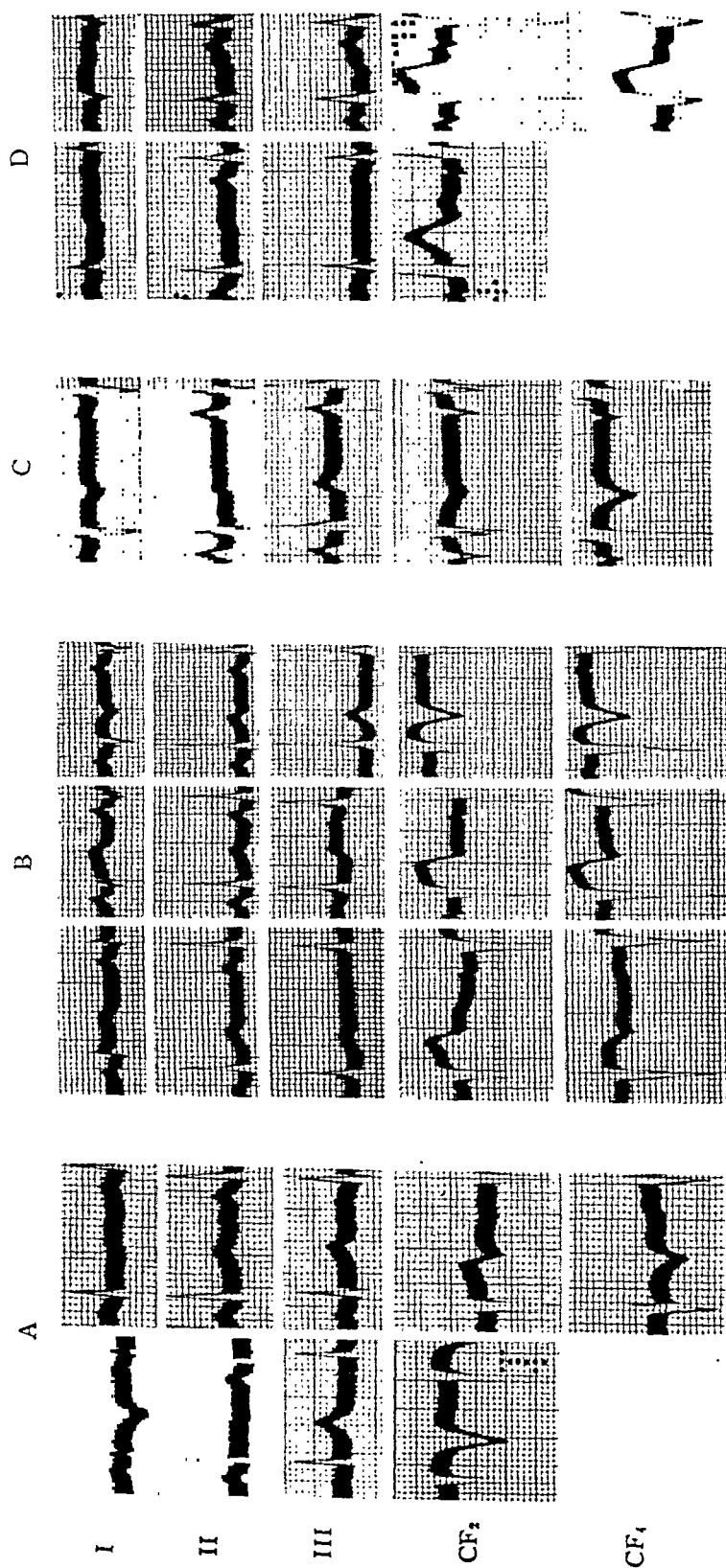
FIG. 7.

and may be the sole QRS pattern residue of an old anterior wall infarct with or without a Q_1 pattern.   On the other hand, the QRS_1 may, during the process of restitution, return to its normal size (figure 7, A).

   D. Type IV QRS Pattern of Anterior Wall Infarction.   In this series 14 cases showed a mainly inverted QRS_1 with an upright QRS_3 (type IV, table 3).   One-half of them (seven cases) showed a Q_1 pattern.   In four others, QRS_1 was entirely inverted with notching on the downstroke, this being considered a variant of the triphasic Q_1 pattern since all four showed a preceding or succeeding triphasic Q_1 type (figure 7, B).   In two other cases, however, QRS_1 was entirely inverted without notching (figure 7, D), and in three others it was associated with a deep S_1.   One of the latter had also P-pulmonale (figure 7, C) [16] and gave a history of long standing bronchiectasis and emphysema; the other two cases with S_1 may also have had QRS_1 inversion on the basis of preëxisting right ventricular preponderance.   It is, of course, difficult to say whether the two cases with QRS_1 entirely inverted and without notching have the significance of a Q or an S wave, although the former seems more likely.   This is substantiated by the fact that one of the cases showing QRS_1 entirely inverted without notching developed this contour only after infarction occurred, and autopsy study of this case revealed · no evidence of right ventricular or any other form of cardiac hypertrophy. Another autopsied case showed a mainly inverted triphasic Q_1 type, and here also no cardiac hypertrophy was demonstrable.   Three other cases of this type showing the triphasic Q_1 pattern had control records taken before the infarction appeared, and all showed normal, upright QRS_1.

   Thus, it would appear that not only the diphasic and triphasic Q_1 patterns are characteristic of anterior wall infarction when QRS_1 is mainly inverted, but that this is true also of the inverted QRS_1 that is notched on the downstroke (figure 7, B) or may even be the case when QRS_1 is inverted and not notched (figure 7, D).   These may all, therefore, be considered as equivalents of the Q_1 pattern.   In the development of none of these patterns is the presence of right ventricular strain essential as shown by both control records and autopsy studies.[17]   None of these QRS_1 patterns should, therefore, be considered as evidence of right ventricular strain in the presence of anterior wall infarction.   When, however, a diphasic QRS_1 with a deep S_1 is present, the problem is more complex (figure 7, C).   We have no evidence to show that infarction will produce this pattern in the absence of preëxisting right ventricular hypertrophy or, at least, a preëxisting normal right axis shift. Nevertheless, although preëxisting right heart strain must be considered, its diagnosis in the presence of an anterior wall infarction demands other evidence than QRS_1 inversion alone.

   E. Type V QRS Pattern of Anterior Wall Infarction.   There were only four cases in this group (type V, table 3) in which QRS was mainly or entirely inverted in all three limb leads (figure 8, C and D).   In three of the four there was an associated low "voltage."   This type with low "voltage"

considered almost pathognomonic of anterior wall infarction by Winter-nitz [61] is thus rare (figure 8, D). In our entire series including all types of infarction only the four foregoing cases were encountered. In one of these, there subsequently developed a superimposed posterior wall infarct pattern, and the limb lead QRS complexes retained their inverted characteristics. No autopsy findings were available in any of these cases.
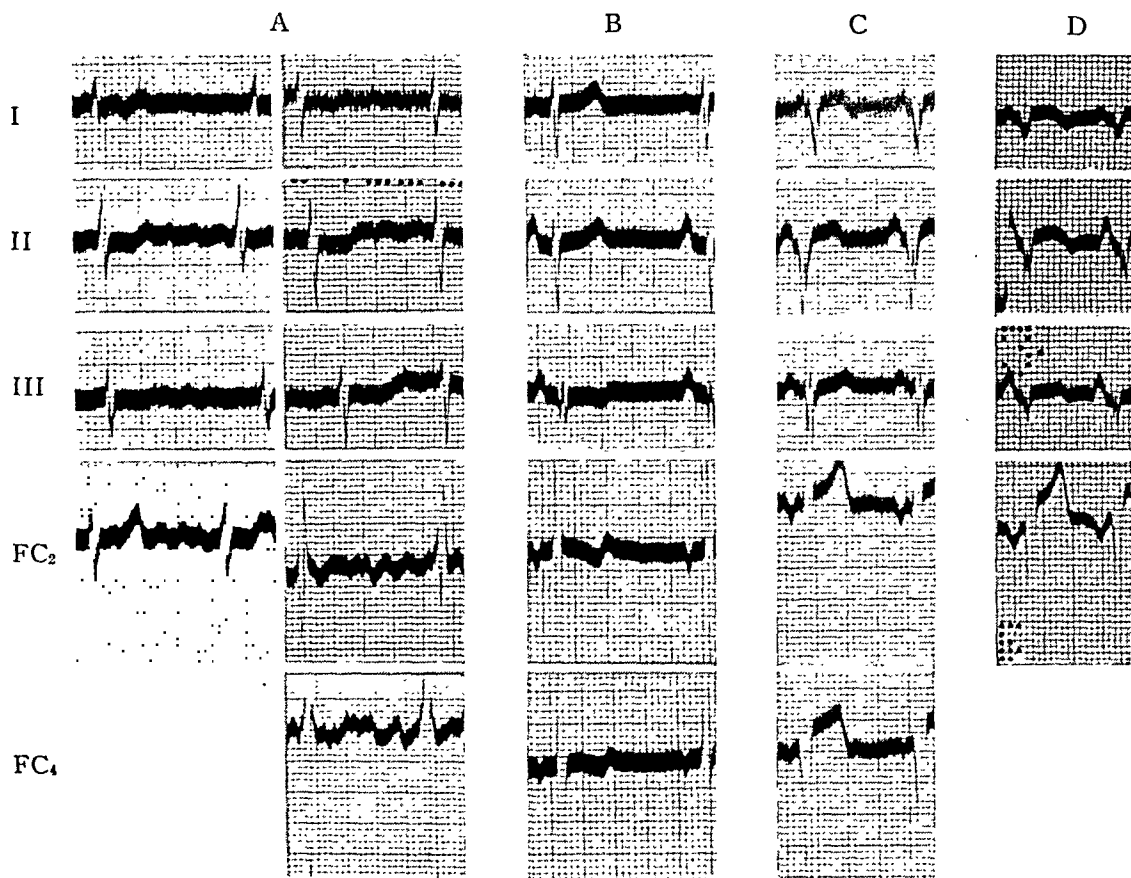
Fig. 8. Two cases of anterior wall infarction (C and D) showing the type V QRS pattern, viz., QRS entirely or chiefly inverted in all the limb leads, and, in addition, two cases of cardiac disease without infarction (A and B) in which a similar QRS pattern is encountered. (Discussed in text.)

A. The two records taken five years apart show the development of mainly inverted QRS complexes in the limb leads in the second record. This is a case of rheumatic heart disease with combined right and left ventricular strain due to a combination of mitral and aortic valvular deformity. Note the presence of deep S waves in the limb leads, and abnormal chest leads in the second record. Both records show auricular fibrillation.

B. From a case of congenital heart disease in a 58 year old man. The chest leads are abnormal but do not indicate infarction. Note the presence of deep S-waves in Leads I and II.

C. Record was taken eight months after a typical clinical attack of myocardial infarction. In addition to having QRS$_1$ and QRS$_2$ entirely inverted (the equivalent of the diphasic Q pattern) the QRS configuration in the chest leads is characteristic also. These QRS changes (type V QRS pattern) are the residue of the anterior wall infarction.

D. Record was taken three days after the development of myocardial infarction. Besides low "voltage," characteristic chest lead and S–T–T configuration, the QRS complexes in the limb leads are entirely inverted and notched (the equivalent of the diphasic Q pattern) and constitute the type V QRS pattern of anterior wall infarction.

Inverted QRS in all three limb leads occurs in circumstances other than anterior wall infarction. In our files it was encountered in congenital heart disease (figure 8, B) and in combined right and left heart strain (figure 8, A). In the cases not due to an anterior wall infarct there are, as a rule, S waves in Leads I and II or in all three limb leads, and, most important, the QRS is of normal "voltage," often being unusually large in cases of congenital heart disease. In the cases due to anterior wall infarction, a Q_1 pattern or QRS_1 entirely inverted is seen (figure 8, C and D). QRS_2 in these cases shows the same configuration as QRS_1. In three of the four cases, QRS_3 was W-shaped (figure 8, C) and in the fourth M-shaped. The presence of this QRS contour in Lead III suggests that the type V QRS pattern is actually indicative of extensive involvement extending to the lateral and posterior walls of the left ventricle, or may even indicate the presence of more than one infarct.[18]

F. Conclusions Concerning QRS Patterns in Anterior Wall Infarction. No one limb lead QRS pattern is found consistently in anterior wall infarction. In fact, in 83 cases neither a Q_1 type nor any of the five other types described was present. Low "voltage" occurred in only one-sixth of the cases, the Q_1 type in a little more than one-fourth of the cases, and intraventricular block in one-sixth of the cases. Aside from the characteristic Q_1 type, the other diagnostic types are the type I QRS pattern which occurs in a little more than one-fifth of the cases and the type V QRS pattern with low "voltage" which is rare (three cases). Other circumstances not related to infarction may give QRS patterns like types I and V. The differentiation is made on the basis of the S–T–T contour in the limb leads, the presence or absence of the Q_1 type, and the QRST configuration in the chest leads and their evolution. The appearance of limb lead QRS contours resembling right, left, and combined heart strain in anterior wall infarction indicates the need of caution in ascribing the contour to heart strain in the

---

Fig. 9. Three cases of anterior wall infarction showing complete restitution except for a residue in the characteristic QRS of the chest leads. Discussed in text.

A. The first record is the control before infarction. The second and third records were taken two days and six months after the development of infarction. The second record is characteristic of anterior wall infarction in all 5 leads and shows, in addition, a small QRS_1 with QRS_2 and QRS_3 upright (type III QRS pattern); QRS_1 is triphasic (W-shaped), the equivalent of the diphasic Q pattern. In the third record all the characteristic QRS and S–T–T contours have disappeared except for the QRS in CF_2 which is entirely inverted and notched on its downstroke.

B. The two records were taken three and one-half months apart, the first during the healing stage of a myocardial infarction. In the first record the S–T–T in the limb leads is characteristic of anterior wall infarction as are the S–T–T and QRS of the chest leads. In the second record all these contours have disappeared except for the QRS in CF_2 and diphasic T in CF_2 and CF_4.

C. The two records were taken 22 months apart, the first during the healing stage of a myocardial infarction. In the first record the five leads are characteristic of anterior wall infarction, the QRS pattern in the limb leads being intermediate between the type I and type II QRS pattern and QRS_1 being the triphasic W-shaped equivalent of the diphasic Q type. In the second record all these characteristics have disappeared, the record being the sort seen in the mixed type of left ventricular preponderance even including the almost entirely inverted QRS in CF_2 which is often found in left preponderance in the absence of infarction.
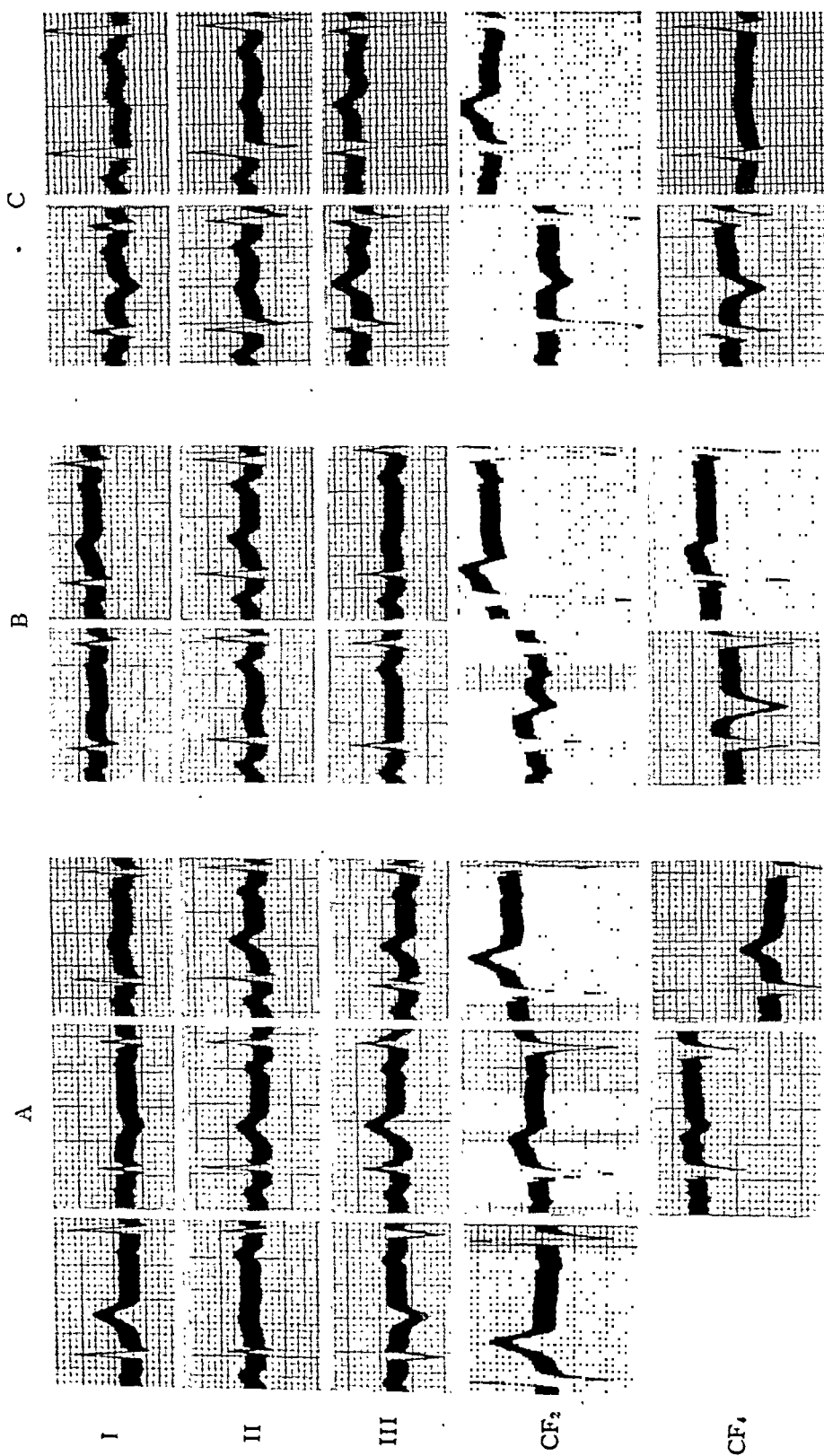
FIG. 9.

presence of infarction, since the evidence presented has indicated that infarction per se may give these patterns. Furthermore, it has been shown in this study that some of the cases showing limb lead QRS changes pointing to these varieties of ventricular strain may be the residue of old anterior wall infarction. The differentiation in such instances is aided by the configuration of the S–T–T complexes in the limb leads, the QRS_1 contour, and the entire ventricular complex in the chest leads, any or all of which may show changes not expected in ventricular preponderance but encountered in stabilized records of old infarction. The changes of the S–T–T segment in the limb leads are familiar, but those in the chest leads merit mention. They consist of T inversion in CF_2 or in CF_2 and CF_4 associated with an upward bowed S–T segment elevated above the isoelectric level (figures 5, A and 7, B).

G. *Chest Lead QRS Patterns in Anterior Wall Infarction.* In only 5 per cent of all the cases of anterior wall infarction were normal QRS complexes encountered in the chest leads (figure 3, A). In the remaining 95 per cent, QRS was abnormal. The abnormalities consisted of (a) entirely inverted QRS (figure 7, B), (b) entirely inverted QRS with a marked notching on the downstroke (figure 9, A and B), (c) diphasic or triphasic QRS with an initial inverted phase of more than 3 mm. (figures 2, A, 3, B, 5, B), and (d) almost entirely inverted QRS of the diphasic variety with the first phase upward but less than 2 mm. in height (figures 2, B, 7, C). The forms (a), (b), and (c) are more characteristic [19] than (d), since the latter is encountered also in left ventricular preponderance (figure 9, C), intraventricular block, and in other circumstances besides anterior wall infarction, especially when only lead CF_2 is involved. It is essential, therefore, that the contour of the QRST be observed as a unit in order to differentiate other conditions from anterior wall infarction.

In the 143 cases having both leads CF_2 and CF_4, 81 showed QRS entirely or almost entirely inverted in both leads, 31 showed this abnormality in lead CF_2 only with lead CF_4 normal, 19 showed the diphasic or triphasic (W) QRS contour with a deeply inverted initial phase, 10 showed no abnormalities of QRS in either lead (although in seven of these the S–T–T was diagnostic of anterior wall infarction), and only two showed a normal QRS in lead CF_2 with an abnormal QRS in lead CF_4. In the 51 cases in which lead CF_2 was the only chest lead taken, 41 had entirely or almost entirely inverted QRS complexes and 10 had diphasic or triphasic (W) QRS complexes with the initial phase deeply inverted. Thus, it is apparent that as far as QRS is concerned, lead CF_2 is far more valuable than lead CF_4 in the diagnosis of anterior wall infarction (figures 2, B, 6, B, 9, A).

The diagnostic value of the chest leads as compared to that of the limb leads is shown further by the fact that in 17 of the 190 cases (9 per cent) of anterior wall infarction, the limb leads showed no specific change in the QRS or S–T–T complexes while the chest leads were pathognomonic; and in only three of the 190 cases (1.5 per cent) were the chest leads normal when

both the QRS and S–T–T were observed, and the diagnosis apparent only in the limb leads.

Summary and Conclusions

1. In an endeavor to increase the diagnostic value of the electrocardiogram, the QRS patterns of 369 series of records with chest leads from cases of definite myocardial infarction were classified.

2. This series included 18 cases of atypical infarction patterns, 20 cases of combined anterior and posterior wall infarction, 141 cases of posterior wall infarction, and 190 cases of anterior wall infarction.

3. Acute diffuse pericarditis complicating infarction was diagnosed in the electrocardiogram in 13 cases; and 41 cases of concordant T-wave inversion in the limb leads (T_N) were encountered.

4. Ninety per cent of the 141 cases of posterior wall infarction showed a Q_3 (or Q_2 and Q_3) or its equivalent. It was concluded that an entirely inverted QRS_3 was equivalent to a Q_3 in the presence of a Q_2 (either a diphasic QRS_2 or a triphasic W-shaped QRS_2 with a deeply inverted initial phase).

5. Only 28 per cent of the 190 cases of anterior wall infarction showed a Q_1 pattern, either with a diphasic or triphasic QRS in this lead. It was concluded that an entirely inverted QRS_1, when notched on the downstroke, was equivalent to a Q_1.

6. The QRS patterns encountered in anterior wall infarction could be grouped into five categories besides a miscellaneous group. These are described.

7. The two most common QRS contours encountered in anterior wall infarction were (a) the small upright QRS_1 (or inverted QRS_1) and (b) the diphasic QRS_2 and QRS_3 with deep S waves. At times each occurred alone without the other; often they occurred together. Thus a small upright or inverted QRS_1 was encountered in 64 of the 190 cases, and diphasic QRS_2 and QRS_3 with deep S_2 and S_3 were encountered in 63 of the 190 cases.

8. These QRS contours in the limb leads can be caused by the anterior wall infarct per se. This was indicated in cases with control records before infarction and in cases checked by necropsy. The occurrence of these QRS contours in the presence of anterior wall infarction, therefore, does not indicate respectively either right ventricular preponderance when QRS_1 is inverted or left preponderance when S_2 and S_3 are present. In such cases these diagnoses should be avoided even though it appears that deep S_2 and S_3 are more apt to be present in cases with preëxisting left ventricular hypertrophy.

9. The combination of a small upright QRS_1 with deep S_2 and S_3, in which QRS_1 was not so large as S_2, was considered especially significant. It constituted the type I QRS pattern of anterior wall infarction and occurred in 35 of the 190 cases. A large number of these cases had intraventricular block (37 per cent as compared to 16 per cent of the entire group of 190

cases). Septal involvement seemed to be responsible for this QRS pattern in some cases, especially since the pattern developed concomitantly with QRS prolongation and disappeared when the QRS duration returned to normal.

10. The presence of deep S_2 and S_3 with QRS_1 of normal amplitude or, at least, larger than S_2 constituted the type II QRS pattern of anterior wall infarction. It occurred in 28 of the 190 cases.

11. In the stabilized stage in both type I and type II QRS patterns, the QRS contour may be the only residue of the old anterior wall infarction. The differentiation of these cases from left ventricular preponderance, aside from the relatively small QRS_1 in the type I pattern, may be difficult or impossible unless some of the characteristic S–T–T changes remain or unless chest leads are taken. Usually, but not always, there is sufficient evidence in the chest leads to warrant the differentiation between left ventricular hypertrophy and an old anterior wall infarction. This is especially important in cases with the type II pattern. In instances showing the type I QRS pattern as a residue, the small size of the QRS_1 should be sufficient to make one consider the existence of some other lesion than an uncomplicated left ventricular hypertrophy.

12. Eleven cases without infarction were encountered (seven with autopsy confirmation) in which a limb lead QRS pattern similar to that of the type I of anterior wall infarction was seen. In these cases the QRS pattern was attributable to combined right and left ventricular strain, alteration in position of the heart, or to a combination of the two. In these cases neither the chest leads nor the S–T–T configuration of the limb leads showed any of the characteristics seen in anterior wall infarction patterns.

13. A small QRS_1 without deep S_2 and S_3 was seen in 15 of the 190 cases of anterior wall infarction. This constituted the type III QRS pattern.

14. A mainly inverted QRS_1 with QRS_3 upright was seen in 14 of the 190 cases of anterior wall infarction. This constituted the type IV QRS pattern and had to be differentiated from right ventricular preponderance on the basis of the limb lead S–T–T pattern, the contour of the QRS and S–T–T of the chest leads, and the presence or absence of a Q_1.

15. An entirely or chiefly inverted QRS in all three limb leads was encountered only four times in the 190 cases of anterior wall infarction. This constituted the type V QRS pattern. In three cases it was considered pathognomonic of the infarction because it was associated with low "voltage." Cases of QRS inversion in the limb leads were encountered in the absence of anterior wall infarction, e.g., in congenital heart disease and in combined right and left ventricular hypertrophy. The characteristic S–T–T infarct contour of both the limb and chest leads as well as the presence of a Q_1 or its equivalent and low "voltage" helps in the differential diagnosis.

16. The chest leads were found to be essential in the diagnosis of anterior wall infarction in 9 per cent of cases in which the limb lead pattern was not characteristic. In only 5 per cent of the cases were the chest leads not characteristic of infarction and the limb leads diagnostic. It was found that in

chest leads CF$_2$ and CF$_4$ the QRS contours most diagnostic of anterior wall infarction were the diphasic QRS with a deeply inverted initial phase, its equivalent, the triphasic QRS with a deeply inverted initial phase, and the entirely inverted QRS with notching on its downstroke. On the other hand, the QRS which is almost entirely inverted with a small initial upright phase is not pathognomonic since it occurs in other conditions besides myocardial infarction. The value of viewing the entire QRST pattern of the chest leads as a unit in diagnosis is emphasized.

17. It is concluded that the QRS pattern is of value in the differential diagnosis in the electrocardiogram of myocardial infarction, and that in doubtful cases it may point to the true cause of the contour seen in the record. This fact in no way depreciates the value of the S–T–T patterns in the diagnosis of myocardial infarction and the utility of the S–T–T evolution in determining whether the infarct is very recent, healing, almost healed, or old. The information obtained by the S–T–T evolution is not replaced by the QRS patterns since these do not undergo such characteristic changes while the infarct is healing.

Addendum. . Attention should be drawn to two communications, bearing on this subject, which appeared while this paper was in press.

The first, a communication from this laboratory (R. Langendorf, M. Hurwitz and L. N. Katz, Brit. Heart Jr., 1943, v, 27), deals in part with the QRS patterns of combined heart strain and supplements the data in this report.

The second, which appeared after our study was completed (S. P. Schwartz and H. Marcus, Am. Rev. Tuberc., 1942, xlvi, 35), reported 15 instances out of 24,200 records in which there was concordant inversion of QRS in the limb leads. Five of these were associated with myocardial infarction, two with congenital heart disease, one with bronchial asthma and bronchiectasis, and seven with chronic pulmonary tuberculosis. Autopsy, obtained in 9 of the 10 cases without myocardial infarction, revealed hypertrophy of the right ventricle in seven cases, the remaining two showed dilatation of the right heart without hypertrophy. These authors stress the rôle of rotation of the heart on its longitudinal axis in causing this peculiar electrocardiographic pattern. Not all their cases fall into the type V QRS pattern of anterior wall infarction described by us; some of the cases illustrated in their paper show a small and diphasic QRS$_1$ (with an S-wave) and would fit into our type I QRS pattern.

BIBLIOGRAPHY

1. (a) BARNES, A. R.: Electrocardiographic patterns, 1940, John C. Thomas, Baltimore.
   (b) BARNES, A. R., and BURCHELL, H. B.: Acute pericarditis simulating acute coronary occlusion, Am. Heart Jr., 1942, xxiii, 247.
   (c) WINTERNITZ, M., and LANGENDORF, R.: Das Elektrokardiogramm der Perikarditis, Acta med. Scandinav., 1938, xciv, 141 and 274.
2. (a) McGINN, S., and WHITE, P. D.: Acute cor pulmonale resulting from pulmonary embolism, Jr. Am. Med. Assoc., 1935, civ, 1473.
   (b) BARNES, A. R.: Pulmonary embolism, Jr. Am. Med. Assoc., 1937, cix, 1347.
   (c) SOKOLOW, M., KATZ, L. N., and MUSCOVITZ, A. N.: The electrocardiogram in pulmonary embolism, Am. Heart Jr., 1940, xix, 166.
3. (a) MASTER, A. M., JAFFE, H. L., and DACK, S.: The heart in acute nephritis, Arch. Int. Med., 1937, lx, 1016.
   (b) LANGENDORF, R., and PICK, A.: Elektrokardiogramm bei akuter Nephritis, Acta med. Scandinav., 1938, xciv, 136.
4. Unpublished observations from this laboratory.

5. (a) ROSE, E., WOOD, F. C., and MARGOLIES, A.: The heart in thyroid disease: II. The effect of thyroidectomy on the electrocardiogram, Jr. Clin. Invest., 1935, xiv, 497.

(b) SPANG, K., and KORTH, C.: Das Elektrokardiogramm bei Überfunktionzuständen der Schilddrüse, Arch. f. Kreislaufforsch., 1939, iv, 189.

6. (a) PARKINSON, J., and BEDFORD, D. E.: Successive changes in the electrocardiogram after cardiac infarction, Heart, 1928, xiv, 195.

(b) LEVINE, S. A., and BROWN, C. L.: Coronary thrombosis: its various clinical features, Medicine, 1929, viii, 245.

(c) PARDEE, H. E. B.: The significance of an electrocardiogram with a large Q in Lead 3, Arch. Int. Med., 1930, xlvi, 470.

(d) FENICHEL, N. M., and KUGELL, V. H.: The large Q-wave of the electrocardiogram. A correlation with pathological observations, Am. Heart Jr., 1931, vii, 235.

(e) WILLIUS, F. A.: Occurrence and significance of electrocardiograms displaying large Q-waves in Lead III, Am. Heart Jr., 1931, vi, 723.

(f) EDEIKEN, J., and WOLFERTH, C. C.: The incidence and significance of the deep Q-wave in Lead III of the electrocardiogram, Am. Heart Jr., 1932, vii, 695.

(g) WILSON, F. N., McLEOD, A. G., BARKER, P. S., JOHNSTON, F. D., and KLOSTERMEYER, L. L.: The electrocardiogram in myocardial infarction with particular reference to the initial deflection of the ventricular complex, Heart, 1933, xvi, 155.

(h) FREUNDLICH, J.: Die klinische Bedeutung der Q-Zacke im Elektrokardiogramm, Deutsch. Arch. f. klin. Med., 1933, clxxv, 129.

(i) BARNES, A. R.: Q and T types of electrocardiograms: their comparative and complementary value in indicating occurrence of acute myocardial infarction, Am. Heart Jr., 1934, ix, 722.

(j) BARNES, A. R.: Correlation of initial deflections of ventricular complex with situation of acute myocardial infarction, Am. Heart Jr., 1934, ix, 728.

(k) DURANT, T. M.: The initial ventricular deflection of the electrocardiogram in coronary disease, Am. Jr. Med. Sci., 1934, clxxxviii, 225.

(l) WINTERNITZ, M.: The initial complex of the electrocardiogram after infarction of the human heart, Am. Heart Jr., 1934, ix, 616.

(m) BARNES, A. R.: Electrocardiogram in myocardial infarction, Arch. Int. Med., 1935, lv, 457.

7. (a) WEINBERG, H. B., and KATZ, L. N.: A common electrocardiographic variant following acute myocardial infarction—the T_N type, Am. Heart Jr., 1941, xxi, 699.

(b) BARNES, A. R., and BURCHELL, H. B.: The significance of negative T-waves in all three standard leads of the electrocardiogram, Jr. Mt. Sinai Hosp., 1942, viii, 346.

8. (a) BARNES, A. R.: Electrocardiographic pattern observed following acute coronary occlusion complicated by pericarditis, Am. Heart Jr., 1934, ix, 734.

(b) LANGENDORF, R.: The influence of diffuse pericarditis on the electrocardiographic pattern of recent myocardial infarction, Am. Heart Jr., 1941, xxii, 86.

9. KATZ, L. N.: Electrocardiography, 1941, Lea and Febiger, Philadelphia.

10. (a) ASHMAN, R., and HULL, E.: Essentials of electrocardiography, 1941, Macmillan, New York.

(b) SODEMAN, W. A., and ENGLEHARDT, H. T.: A QRS pattern of diagnostic value in the electrocardiogram, Am. Jr. Med. Sci., 1940, cc, 337.

(c) PARDEE, H. E. B.: Clinical aspects of the electrocardiogram, 1941, Paul B. Hoeber, New York.

(d) HOLZMANN, M.: Klinische Erfahrungen mit elektrokardiographischen Brustwandableitungen, Arch. f. Kreislaufforsch., 1937, i, 2.

(e) JERVELL, A.: Elektrokardiographische Befunde bei Herzinfarkt, Acta med. Scandinav., 1938, Supp. 68, pp. 1 to 267.

11. KAPLAN, L. G., and KATZ, L. N.: The characteristic electrocardiograms in left ventricular strain with and without axis deviation, Am. Jr. Med. Sci., 1941, cci, 676.

12. (a) KATZ, L. N., SANDERS, A., MEGIBOW, R. S., and CARLEN, S.: Heart size and experimental atheromatosis in the rabbit, Am. Jr. Med. Sci., 1940, cc, 731.

(b) PALMER, J. H.: Size of heart after coronary thrombosis, Canad. Med. Assoc. Jr., 1937, xxxvi, 387.

(c) HURWITZ, M. M., and FRIEDBERG, L.: The relationship of heart size to cholesterol content in experimental atheromatosis in the rabbit, Arch. Path., 1942, xxxiv, 875.

13. SODEMAN, W. A., and BURCH, G. E.: Left axis deviation in dropped heart, Am. Heart Jr., 1938, xv, 490.

14. WILSON, F. N.: The occurrence in angina pectoris of electrocardiographic changes similar in magnitude and in kind to those produced by myocardial infarction, Am. Heart Jr., 1941, xxii, 64.

15. (a) ERLANGER, H., ROSENBAUM, F. F., COTRIM, N., JOHNSTON, F. D., and WILSON, F. N.: The form of the dog's precordial electrocardiogram in bundle branch block complicated by anterior infarction, Jr. Clin. Invest., 1941, xx, 460.

(b) WILSON, F. N., JOHNSTON, F. D., and BARKER, P. S.: Electrocardiograms of an unusual type in right bundle branch block, Am. Heart Jr., 1934, ix, 472.

(c) BOHNING, A., and LANGENDORF, R.: Unpublished data in preparation.

16. WINTERNITZ, M.: Zur Pathologie des menschlichen Vorhofelektrokardiogramms, Med. Klin., 1935, xxxi, 1575.

17. KLAINER, M. J.: The prognostic significance of right axis deviation in arteriosclerotic and hypertensive heart disease, Am. Jr. Med. Sci., 1940, cxcix, 795.

18. BOHNING, A., and KATZ, L. N.: Four lead electrocardiogram in cases of recent coronary occlusion, Arch. Int. Med., 1938, lxi, 241.

19. (a) LANGENDORF, R., and PICK, A.: Zur Diagnose des Myokardinfarktes mit Hilfe von Brustwandableitungen, Acta med. Scandinav., 1938, xcvi, 80.

(b) MORTENSEN, V.: The QRS complex in precordial leads in anterior wall infarction. True and false infarction curves, Am. Jr. Med. Sci., 1941, cci, 349.

MYO–EPITHELIAL HAMARTOMA OF THE GASTRO-INTESTINAL TRACT (CLARKE) *

By Nathan Mitchell, M.D., and Alfred Angrist, M.D.,
Jamaica, Long Island, New York

The finding of small masses of aberrant epithelial and muscular tissue in various portions of the gastrointestinal tract is not uncommon. The nomenclature of these nodular growths has varied according to the amount and character of the epithelium and its resemblance to known viscera. Thus the large majority of the ectopic foci have been called aberrant or accessory pancreatic tissue, while other designations include "adenomyoma," "Brunner's adenoma," and "incompletely differentiated accessory pancreas." In 1940 Clarke suggested the term "myo-epithelial hamartoma" as an all-inclusive one, to cover all such nodular masses of developmental origin. This designation seems the most applicable. Twenty-four instances of ectopic tumor-like foci will be presented, illustrating variations in epithelial and muscle components, and justifying the use of the term "myo-epithelial hamartoma."

Literature: Complete reviews of the reported cases of aberrant pancreatic tissue have been recorded by Branch and Gross,[1] Pappi,[2] and most recently by Faust and Mudgett.[3] The latter authors have outlined the incidence and sites of occurrence of the nodules. The most frequently involved parts of the gastrointestinal tract are the duodenum (28.37 per cent), the stomach (25.67 per cent) and the jejunum (17.56 per cent). Since the publication of their review several isolated case reports have appeared. From the available literature, there have been collected nine additional cases in the stomach, three in the duodenum, two in the gall-bladder, two in Meckel's diverticula, and one in the jejunum.[4-20] It should be emphasized at this point that the literature cited above refers distinctly to cases of "aberrant pancreatic tissue." In addition to these reports, Clarke [21] added eight instances including four gastric masses, and one each in a Meckel's diverticulum, jejunum, duodenum and gall-bladder. He included adenomyoma as well as aberrant pancreatic tissue. Hintzsche [22] identified isolated islands of cells in the duodenal mucosa as of pancreatic origin. He employed Pappenheim's stain on formalin fixed tissue, and claimed to see nuclei, cytoplasmic granules and fibrillation of the basilar cytoplasm identical with that of pancreatic cells.

In addition to the value of careful recording of incidental postmortem findings, certain important features of immediate clinical application have been stressed by various authors. Thus, the nodules occurring in the region of the pylorus have given rise to symptoms of obstruction.[7] Polypoid tumors have been visualized by roentgenogram of the stomach and duodenum.[15] At

operation the nodules have been mistaken for malignant tumors, and needless radical surgical procedures have been carried out.[6] Ulceration at the surface of a duodenal nodule has been recorded.[8] Symptoms of hypoglycemia have been attributed to a nodule showing abundant circumscribed islet tissue as well as islet cells diffusely scattered throughout the mass.[20] Intussusception of the ileum at the site of a Meckel's diverticulum which bore a mass of aberrant pancreatic tissue at its apex, has been seen.[5]

Of the histological features of note, typical islands of Langerhans have been seen on numerous occasions. Branch and Gross report islet tissue in nine of their 24 cases. In the pyloric masses glandular tissue closely resembling Brunner's glands is not uncommon.

It will be noted that in the cases reported below, masses occurring in the gastrointestinal tract permit of division into two groups. The first shows typical pancreatic tissue. In the second group the aberrant tissue consists of intermingled smooth muscle and epithelial duct structures.

CASE REPORTS

Case 1. M. L., a 69 year old female, presented the picture of thrombosis of the left middle cerebral artery with extensive encephalomalacia. In the pyloric region a large mass 4 by 1.5 cm. was noted involving the deeper layers of the mucosa extending to the subserosa (figure 1). A small amount of smooth muscle, extensive areas of hyalinization, neurofibromatous elements, and a large dilated duct, were prominent features in the mass.

Case 2. H. S., a 62 year old female, suffered from repeated episodes of ascites, and finally succumbed with a terminal picture of cholemia. A small fluctuant yellow mass resembling a dilated lacteal was seen in the submucosa of the duodenum (figure 2). Pancreatic acini, ducts, and hypertrophic islet tissue were seen separating the layers of the duodenum on microscopy.

Case 3. E. S., a 13 year old female, was operated upon because of symptoms and signs of acute appendicitis. Laparotomy revealed a large Meckel's diverticulum. At the base of the diverticulum a heaped-up granular mucosa resembling gastric mucosa was seen. Distal to this, in the subserosal fat tissue, a firm, grayish trabeculated mass was apparent (figure 3). Microscopic examination of the mass revealed dilated ducts, acinar tissue, and typical pancreatic islets of Langerhans.

Case 4. J. H., a 53 year old female, died with a picture of cachexia after a downward course. Carcinoma of the ovary with widespread metastases was found. A firm white mass 2 by 1 cm. was noted at the fundus of the gall-bladder (figure 4). Dilated ducts and smooth muscle fibers were seen separating the bundles of the muscular wall.

Case 5. M. C., a 48 year old colored female, entered with complaints of herpes zoster of the skin of the thorax, and anemia. At autopsy, generalized Hodgkin's disease was found. A mass measuring 0.5 by 0.5 cm. was seen in the submucosa of the jejunum 10 cm. from the ligament of Treitz. On section, the mass resembled normal pancreatic tissue. Microscopically, islet tissue, acini, and ducts containing eosinophilic inspissated secretion were seen. Metaplasia of the acinar to islet tissue was suggested (figure 5).

Case 6. A. T., a white female infant, suffered extensive birth trauma and died in two months with hydrocephalus. A rounded mass 3 mm. in diameter was seen in the region of the pylorus. Microscopically, large ducts were seen which blended with glands showing typical features of Brunner's glands (figure 6). Suggestive acinar

Fig. 1. *Case 1.* Adenomyoma of pylorus extending throughout all layers of gastric wall with some fixation and smoothness to overlying mucosa. Serosal aspect of this mass measured 4 by 1.5 cm. (× 2.)

tissue was noted near the mucosa of the stomach. Xanthomatous areas were seen in the muscularis.

Case 7. L. B., a 64 year old male, died after thyroidectomy, the immediate cause of death being congestive heart failure. A small nodule 0.5 by 0.5 cm. was found in the ileum six inches from the ileocecal valve. The gross diagnosis was leiomyoma. Microscopically, a large amount of smooth muscle was seen, in which were embedded large ducts (figure 7), many containing papillations. No islet tissue was found.

Case 8. F. N., a white female infant, died after nine hours with the clinical picture of hydrops neonatorum. A small nodule was detected in the duodenum ½ cm. above the ampulla. This was composed of dilated duct structures surrounded by muscle.

Case 9. T. C., a 49 year old white female, exhibited the classical symptoms and signs of massive cerebral hemorrhage. In the jejunum 15 cm. from its origin, a mass measuring 2 by 1.5 cm. was seen in the submucosa, extending to the subserosa. Typical elements of pancreatic tissue were seen microscopically, including acini, ducts, and islet tissue.

Case 10. R. R., a 67 year old male, died of hypertensive heart disease with congestive heart failure. A mass 2 by 2 cm. was found in the duodenum 4 cm. from the pylorus. Ducts, acini and a small amount of islet tissue were identified. In some

areas the epithelium of the acini was atrophic and seemed to merge imperceptibly with definite nerve bundles.

Case 11. B. B., a 71 year old male, died of the effects of coronary thrombosis. At autopsy, a firm nodule with cystic zones was seen in the fundus of the gall-bladder. Dilated ducts were noted in the muscular layer, presenting a well circumscribed mass.

FIG. 2. *Case 2.* Nodular submucosal mass of pancreatic tissue in the duodenum. (× 4.)

Case 12. C. S., a 34 year old white female, entered with symptoms of congestive heart failure and died with a diagnosis of malignant nephrosclerosis. In the first part of the duodenum, distinct from the pancreatic head, there was seen a firm mass 2 by 2 cm. Acinar tissue, ducts, and islet tissue were noted in their usual proportion.

Case 13. C. B., a 40 year old white male, was admitted with a fractured tibia, and while on the ward died from a large thrombus of the left coronary artery. A firm mass 1 cm. in diameter was noted at the fundus of the gall-bladder, which on section revealed cystic areas corresponding to dilated duct structures. A small amount of muscle was seen.

<div>Fig. 3.</div>
<div>Fig. 4.</div>

FIG. 3. *Case 3.* Resected Meckel's diverticulum showing triangular mass of differentiated pancreatic tissue at summit of diverticulum in subserosa. Note sharply delimited area of ectopic gastric mucosa below the pancreatic mass. ($\times$ 4.)

FIG. 4. *Case 4.* Cystic adenomyoma at fundus of gall-bladder. ($\times$ 1.5.)

Case 14. M. W., a 68 year old white female, entered with signs of a generalized peritonitis. At laparotomy a ruptured gall-bladder was found, and the patient died soon after operation. A small mass 0.5 by 0.5 cm. was found at the ampulla of Vater. Microscopically, ducts lined by tall cuboidal epithelium were seen embedded in dense collagenous tissue. The entire ectopic mass was located in the submucosa, and had apparently caused obstruction.

Case 15. T. C., a 55 year old male, was struck by an auto, and died of extensive skull fracture and epidural hematoma. A small nodule in the subserosa of the fundus of the gall-bladder was observed, and contained dilated duct structures mingled with atrophic bundles of smooth muscle.

Case 16. A. C., a 30 year old male, entered the hospital in uremia. At autopsy, large white kidneys of subacute glomerulonephritis were found, in association with subacute bacterial endocarditis. On the posterior wall of the duodenum, above the

FIG. 5. *Case 5.* Differentiated pancreatic tissue in submucosa of jejunum. Note preserved lobulation. Mucosa and lumen above. ($\times$ 175.)

FIG. 6. *Case 6.* Aberrant glandular and muscle tissue with transition from duct structure to Brunner gland-like nests. (× 500.)

FIG. 7. *Case 7.* Adenomyomatous mass showing marked fibrosis, located between longitudinal and circular muscle planes of wall. Serosa seen below. (× 300.)

ampulla, a small mass 0.5 by 0.5 cm., with overlying ulceration, was seen. Acini and ducts were identified, but no islet tissue was seen.

Case 17. L. S., a 37 year old female, died of extensive tuberculous meningitis. A nodule measuring 1 by .5 cm. was noted in the submucosa of the jejunum. Characteristic pancreatic tissue was seen, with no islet tissue.

Case 18. D. B., a 62 year old male, entered the hospital with severe jaundice, and at autopsy a subacute yellow atrophy of the liver was found. In the fundus of the gall-bladder a mass 0.7 by 0.5 cm. was seen, which contained large ducts enmeshed in thin strands of smooth muscle.

Case 19. T. B., a 62 year old male, died of hypertensive heart with congestive failure. A small cystic mass was found in the subserosa at the fundus of the gall-bladder.

Case 20. C. C., a 53 year old white male, died of chronic myelogenous leukemia after a prolonged downward course. In the proximal portion of the ileum, a small nodule 1 by 0.5 cm. was found in the submucosa. Duct structures with cystic dilatation were seen interspersed among hypertrophied and distorted muscle bundles.

Case 21. A. F., a 45 year old male, died shortly after the onset of severe precordial pain, and showed extensive myocardial infarction at autopsy. A nodule 1 cm. in diameter was found at the pylorus in the submucosa. Microscopically this consisted of acinar tissue and dilated ducts. No islet tissue was seen.

Case 22. M. B., a 62 year old female, died of generalized peritonitis following an attempt at end to end anastomosis of the sigmoid after resection of a perisigmoidal abscess caused by ruptured diverticulitis. A firm nodule 1.5 by 1 cm. was observed at the pylorus. All of the components of normal pancreatic tissue, including islet tissue, were seen.

Case 23. M. W., a 78 year old white female, died shortly after admission for generalized peritonitis due to a ruptured diverticulitis of the sigmoid colon. The fundus of the gall-bladder presented a small mass in the muscularis which revealed dilated duct structures surrounded by a sparse amount of smooth muscle.

Case 24. E. E., a 50 year old colored male, died after a long period of hospitalization, with terminal cachexia due to carcinomatosis. A firm nodule was found in the proximal ileum, measuring 1 by 1 by .5 cm. The mass occupied the submucosa, muscularis and subserosa. Hypertrophic muscle bundles were seen in which were interspersed varying sized ducts, in the largest of which intraductal papillary epithelial proliferation was noted.

DISCUSSION

Division of the 24 cases into two groups is indicated in table 1. The distribution of the aberrant pancreatic tissue conforms closely to that ob-

TABLE I

Distribution of Gastrointestinal Myo-Epithelial Hamartoma

A. Aberrant Pancreas . 11

```
┌ Pylorus ............ 2 ┐
│ Duodenum .......... 4 │   With islet tissue .......... 7
┤ Jejunum ........... 2 ├   Without islet tissue ........ 4
│ Ileum ............. 2 │
└ Meckel's diverticulum . 1 ┘
```

B. Adenomyoma 13

```
┌ Gall-bladder ........ 7 ┐
│ Duodenum .......... 1 │   With chronic cholecystitis .. 1
┤ Ampulla of Vater .... 1 ├   Without chronic cholecystitis 6
│ Pylorus ........... 2 │
└ Ileum ............. 2 ┘
```

TABLE II

Résumé of 24 Reported Cases

Case No.	Age	Sex	Location	Size	Fibrosis	Islet	Epithelial Components	Muscle Component	Remarks
1	69	F	Pylorus, mucosa, submucosa	0.4 by 1.5	++++	–	Cystic duct structure	Little hyalinization nerve elements extending into mucosa	Inflammation; giant cells
2	62	F	Duodenum, submucosa muscle	0.9 by 0.9	++	+	Acini, ducts	Hypertrophy	Hypertrophy of islets
3	13	F	Meckel's diverticulum, sub-serosa	1 by 1 by 1	++	+	Acini, ducts with dilatation	—	Ectopic gastric mucosa; operative specimen; Chronic cholecystitis
4	53	F	Gall-bladder. Fundus muscle	2 by 1	–	–	Ducts (dilated)	Some	
5	48	F	Jejunum. Submucosa	0.5 by 0.5	–	+	Acini, ducts	—	Inspissated secretion in ducts, metaplasia of acinar to islet tissues
6	2 mo.	F	Pylorus. Submucosa muscle	0.3 by 0.3	–	–	Ducts, acini (?) Brunner's glands	Xanthoma-like areas	
7	64	M	Ileum. Submucosa	1.5 by 0.5	+++	–	Acini (atrophic), ducts with papillation	Much hypertrophy	Resembled leiomyoma in gross
8	9 hrs.	F	Duodenum. Submucosa muscle	0.2 by 0.3	–	–	Ducts	Little	
9	49	F	Jejunum. Subserosa	1.5 by 2	+	+	Acinar tissue, ducts	Little; distortion	Interstitial pancreatitis in aberrant nodule
10	67	M	Duodenum. Submucosa and subserosa	2 by 2	–	+	Acini, ducts	Hypertrophied	Merging of nerve and epithelial tissue (micro.)
11	71	F	Gall-bladder. Fundus	1 by 0.5	–	+	Ducts (cystic)	Little	No cholecystitis
12	34	F	Duodenum. Subserosa	2 by 2	–	+	Acinar tissue, ducts	Distorted; some hypertrophy	
13	40	M	Gall-bladder. Fundus	1 by 1	+++	–	Ducts with some cystic dilatation	Little	No cholecystitis
14	68	F	Duodenum. Submucosa	0.5 by 0.5	++++	–	Ducts	Hypertrophy; some distortion	Empyema of gall-bladder with peritonitis
15	55	M	Gall-bladder. Fundus	0.5 by 0.5	–	–	No sections	—	No cholecystitis
16	30	M	Duodenum. Submucosa submucosa	0.5 by 0.5	+++	–	Acini, ducts	Little	Ulceration
17	37	F	Ileum. Submucosal muscle	1 by 0.5	–	–	Acini, ducts	Some	
18	65	M	Fundus	0.7 by 0.5	–	–	Ducts with dilatation	Hypertrophied; distorted	
19	62	F	Gall-bladder. Fundus	1 by 1	–	–	Ducts with dilatation		No cholecystitis
20	53	M	Ileum. Submucosal muscle	1 by 1	+	–	Ducts with cystic dilatation and cystic intra-ductal papillomatous proliferation		No cholecystitis
21	45	M	Pylorus. Submucosa	1 by 1	+	+	Acini, ducts with dilatation	Hypertrophy	No cholecystitis
22	62	F	Pylorus. All coats	1.5 by 1 by 8	++	+	Acini, ducts with dilatation	Hypertrophy	Acute inflammation
23	78	F	Gall-bladder. Fundus	Small			(No sections)	—	
24	50	M	Ileum. Submucosa	1 by 1 by 0.5	–	–	Acini	Hypertrophy	

served by other writers. The adenomyoma group of lesions predominates in the gall-bladder. The absence of inflammatory lesions in the wall of the gall-bladder is worthy of note. It is suggested that the single instance in which chronic cholecystitis was found represents a coincidental lesion. Table 2 offers a résumé of clinical and pathological features of the cases in this series.

The complications noted in this series were those of obstruction, ulceration, and inflammation. In case 2 a nodule strategically situated at the ampulla of Vater was accompanied by marked fibrosis, with stenosis and obstruction at the ampulla. An ascending cholangitis, with empyema of the gall-bladder, rupture, and generalized peritonitis, was the direct result of the obstructing tissue mass. In case 14 large numbers of inflammatory cells were seen in the pyloric mass. In addition to acute catarrhal inflammation of the duct structures in the nodule seen in case 24, a diffuse exudative inflammatory change was seen in the muscle. In case 16, an ulceration .5 cm. in diameter was observed at the summit of the nodule located in the submucosa of the duodenum. The latter three cases were unaccompanied by symptoms attributable to the masses.

The nodules showed histological features characteristic of normal pancreas. Zymogen granules were occasionally prominent. Direct transition of duct structures to Brunner-like glands was noted in case 6. Histopathological features commonly seen in the normally situated pancreas were encountered in the ectopic foci. Thus, chronic interstitial inflammation was seen in case 4, and inspissated eosinophilic secretion within dilated duct structures, and metaplasia of acinar to islet tissue were observed in case 12. Of interest was the observation in case 10 of focal atrophic changes in the acini with simulation of nerve structure in cross section. Epithelial hyperplasia with papillary infolding of duct epithelium was seen in case 24.

The muscular component was variable in amount and orientation. In many cases, such distortion had taken place that it could not be ascertained whether or not the muscle was an integral part of the nodule or merely residual or hypertrophic muscle of the intestinal tract. In case 6 a small zone of "xanthoma" cells was seen deep in the muscle tissue. Extensive hyaline change of muscle tissue was noted in the large pyloric mass in case 14. In this same case, neurofibromatous-like proliferation of nerve structures was seen penetrating into the gastric mucosa. In case 13, the muscle tissue was particularly abundant, leading to the erroneous diagnosis of leiomyoma in the gross. Most of the masses in the gall-bladder, in contrast, contained thin atrophic strands of muscle, and some epithelial structures were dilated with the appearance of miniature cysts.

The finding of both aberrant fully developed pancreatic tissue and ectopic gastric mucosa in a Meckel's diverticulum in case 23 parallels the case reported by Black and Packard.

The theories of formation of islands of aberrant tissue in the gastrointestinal tract have been reviewed by Branch and Gross, and by Clarke.

Most authors subscribe to the theory of inclusion of epithelial islands from the region of the embryonic foregut. Whether this explanation does apply to all the gall-bladder nodules is open to question. The finding of muscle elements has been attributed to similar inclusion of embryonal muscle cells at the time of separation of the epithelial focus. The possibility that the muscle components represent hypertrophic changes in the muscles of the wall of the involved portion of the intestine cannot be ruled out in all cases.

If it is assumed that the masses described above are of embryonic origin, and that the aberrant epithelial tissue is capable of differentiating into many different forms of glandular structures, then the term "myo-epithelial hamartoma" should be applied. In the adenomyomatous nodules, the duct structures resemble closely pancreatic and bile ducts, and may represent displacement of the latter during development. Although the distinct possibility exists that the appearance of adenomyoma may be simulated by widespread atrophy of acinar tissue in an aberrant pancreatic mass, no such complete transformation has been demonstrated. In one instance, localized atrophy of this nature was noted.

CONCLUSIONS

1. Twenty-four cases of aberrant nodular masses of ectopic differentiated epithelium and muscle in the gastrointestinal tract are described.

2. The variations in the epithelial structures and muscle tissue are indicated.

3. It is suggested that Clarke's designation of such masses as "myo-epithelial hamartomas" be adopted.

BIBLIOGRAPHY

1. BRANCH, C. D., and GROSS, R. E.: Aberrant pancreatic tissue in the gastrointestinal tract: report of 24 cases, Arch. Surg., 1935, xxxi, 200–224.

2. PAPPI, ARRIGO (quoted by DANZIS): Sui pancreas aberranti rivista sintetica complete e contributo casistico, Arch. ital. d. mal. d. app. diger., 1935, iv, 534–579.

3. FAUST, D. B., and MUDGETT, C. S.: Aberrant pancreas, with review of the literature and report of a case, ANN. INT. MED., 1940, xiv, 717–728.

4. LAPIDARI, M.: Pancreas accessorio dello stomaco, metaplasia eterotopica a tipo pancreatico-della mucosa gastrica? Arch. ital. d. chir., 1937, xlvii, 432–452.

5. BLACK, W. C., and PACKARD, G. B.: Surgical complications resulting from the presence of heterotopic tissue in Meckel's diverticulum, Rocky Mountain Med. Jr., 1938, xxxv, 859–863.

6. DANZIS, M.: Aberrant pancreatic tissue in the gastro-intestinal tract; report of two cases and review of literature, Surg., Gynec., and Obst., 1938, lxvii, 520–525.

7. PICCO, A.: Adenoma pilorico associato a pancreas aberrante, Arch. ital. d. anat. e istol. pat., 1938, viii, 632–637.

8. GUIDOTTI, C.: Pancreas accessorio della parete duodenale e sua imagine radiologica, Arch. di radiol., 1939, xv, 34–36.

9. CRUIKSHANK, M. M.: Aberrant pancreatic tissue in the alimentary tract, Indian Med. Gaz., 1939, lxxiv, 74–75.

10. SAUPE, E.: Über einen durch ein Nebenpankreas hemorgerufenen Magenpolypen, Med. Klin., 1939, xxxv, 384–385.

11. Picco, A.: Adenoma pancreatico della parete gastrica, Arch. ital. d. chir., 1939, lv, 532–541.
12. Martin, J. F., and Guichard, A.: Contribution à l'étude anatomo-pathologique des pancreas aberranti due tube digestif. A propos de deux observations ineditia, Jr. de méd. de Lyon, 1939, xx, 599–610.
13. Masciottra, R. L., and Urquiza, S. Vinas: Pancreas duodenal aberrante, Arch. argent. de enferm. d. ap. digest. y de la nutricion, 1940, xvi, 478–483.
14. Granet, E.: Aberrant pancreas simulating gastric neoplasm, Med. Rec., 1940, cli, 125–126.
15. Picchio, C.: Nodulo aberrante di pancreas nella parlte dello stomaco, Radiol. med., 1940, xxvii, 52–53.
16. Thorsness, E. T.: An aberrant pancreatic nodule arising on the neck of a human gall bladder from multiple outgrowths of the mucosa, Anat. Rec., 1940, lxxvii, 319–333.
17. Jacobson, A. S.: Accessory pancreas in the wall of the gall bladder, Arch. Path., 1940, xxx, 908–910.
18. Kreig, E. G.: Heterotopic pancreatic tissue producing pyloric obstruction: a review and case report, Ann. Surg., 1941, cxiii, 364–370.
19. Cabot Case 37182: New England Jr. Med., 1941, ccxxiv, 774–776.
20. Smith, F. G.: Aberrant pancreatic tissue with hyperinsulinism, Jr. Am. Med. Assoc., 1942, cxviii, 454–455.
21. Clarke, B. E.: Myo-epithelial hamartoma of the gastrointestinal tract, a report of eight cases with comment concerning genesis and nomenclature, Arch. Path., 1940, xxx, 143–152.
22. Hintzsche, E.: Über verstreute Pankreaszellen in der Duodenalschleimhaut, Ztschr. f. mikr.-anat. Forsch., 1939, xlix, 271–274.

THE CULTIVATION OF PHYSIOLOGICAL RELAXATION *

By Edmund Jacobson, M.D., F.A.C.P., *Chicago, Illinois*

A PERUSAL of medical journals today, as compared with a decade ago, indicates a growing recognition of the problems of relaxation. Most commonly it is linked with the discussion of hyperemotional states, noted when the patient is excitable, fatigued or hypochondriac; the need of "calmness and poise" is being stressed in a variety of disorders so wide as to include not only essential hypertension, coronary occlusion, bronchial asthma and neuropsychiatric states but also spastic colitis and even common forms of constipation.[1]

Knowledge of the problem of relaxation would seem to be spread wide, but extremely thin, in the sense that the physiological aspects of this difficult subject receive scant current attention. It is not commonly realized how well defined and also how technical the field has become. Many physicians still think of relaxation in terms of hobbies, sports or warm baths, and they believe that daily rests are the most effective measure available for the reduction of nervous irritability and fatigue states. Recent investigations fail to support this belief and have called attention once more to the diminution of neuromuscular hypertonia and residual tension as the distinguishing mark of physiological relaxation.[2] This accords with previous clinical studies, which suggested that relaxation can be cultivated in patients to replace states of excitement, emotion or neuromuscular hypertension.[3] Measurement of neuromuscular states in patients, before and after training to relax, confirmed this suggestion. Evidence has been growing that a greater reduction of nervous irritability and of fatigue states is secured if relaxation is cultivated according to physiological methods.[4]

This procedure is carried out along pedagogical lines similar to those followed in schools and colleges in teaching other skills. ·Methods of suggestion as practiced in psychotherapy are strictly avoided. After each period of instruction which lasts about 50 minutes, the patient customarily practices at home for like periods.

In most instances, the patient is requested to live a full, normal life, rather than to reduce his working hours. Unless it is necessary, the physician does not advise him to "go slowly," or to avoid rush and strain, since the purpose of treatment is to enable him to meet his environment rather than to escape from it. Only in cardiac and other dangerous organic conditions are the range and character of daily activities generally limited.

In acute cases of nervous disturbance, one or two treatments may be indicated to reduce the reactions. The results may then resemble those fol-

lowing the brief administration of sedatives. Inspection of the excited patient reveals when and where he is excessively tense in his skeletal musculature. The attending physician points out these regions and leads the individual to note what he is doing muscularly. He shows him where and how he is maintaining his nervous excitement by his own voluntary muscular activity. Under direction, the patient increases the tensions noted; for example, if he is frowning excessively, he increases the act till he becomes clearly aware of it. Thereupon he is instructed to discontinue what he was doing, both (1) abruptly and (2) slowly and progressively. Repeated practice is given until the over-active muscle groups have evidently become more relaxed.

In chronic conditions, the procedure follows an anatomical order, including the chief muscle groups of the limbs, trunk, neck and head. This order is often as follows: Left arm flexors, left arm extensors, left wrist flexors, left wrist extensors, right arm similarly, left foot flexors, left foot extensors, left leg flexors, left leg extensors, left thigh flexors, left thigh extensors, abdominal group, back extensor group, respiratory muscles, shoulder retractors, pectoral group, shoulder elevators, neck groups, frontalis (wrinkling), corrugator (frowning) lid and eye muscles, facial muscles, speech muscles. Those of the eyes and speech require most detailed instruction, for these participate characteristically in mental activities. Physiological evidence has supported the view that fears and anxious mental states can be relaxed away.

The patient can learn to recognize when and where he is tense if he observes carefully while he contracts the chief skeletal muscle groups one at a time during successive periods of instruction. For example, during the first period, after he has been lying quietly with eyes closed for about five minutes, he bends the left arm at the elbow, noting the sensation from muscular contraction in the flexor muscles. He is then requested to discontinue what he has been doing until no trace of this sensation remains. As a rule most of the first hour of instruction is devoted to repeated contraction and relaxation of the muscles that flex and extend the left arm. When tension has once been recognized in these localities, it becomes easier to recognize the same sensation elsewhere as a guide to relaxation.

Drill is required before the patient learns to distinguish between sensations of muscular contraction ("tenseness") and other classes of sensations, particularly those from tendons and joints. He observes that whenever and wherever he contracts, it is he who is doing it: there is always effort; but if he discontinues that doing, it is the negative of effort. The novice, however, wrongly tries to relax with effort, but in so doing, he contracts muscles, thereby frustrating his aim. In the same way the insomniac and the nervous person, incessantly seeking comfort through a series of efforts, perpetuate their own overactive states.

In medical practice, the patient may be nervously reëducated in the manner sketched above over a period of months or longer. The sedative habit

is broken. It may require 18 months to train a fatigued or nervous patient to the point where electrical records indicate an habitual state of relaxation in most skeletal muscles. However, it is customary to devote the second half of this training to the sitting position, in order to condition him so that he may become less tense and less excitable during his daily pursuits.

The scientific understanding of procedures employed in disease requires that they be tested also under normal physiological conditions, if possible. Accordingly, we here inquire whether neuromuscular relaxation can be cultivated in states of health.

For this investigation, seven individuals were available, women instructors in physical education (Y. W. C. A.) excepting one, who was a physiotherapist. Their ages varied from about 22 to 40 years. Four of the seven were single. All appeared to be in normal spirits, able to "relax" in the sense employed in the gymnasium, but none had received technical training in physiological relaxation. Accordingly, they registered for a course of instruction, affording opportunity for the present study, the purpose of which they did not know.

All tests were performed in a quiet room in the sitting posture, while the subject read a current periodical in good light. No exchange of words occurred once the test was begun. The left foot was supported on a rest, whereas the right hung freely. Finely pointed platinum iridium wires, 0.011 inch in diameter, were employed as electrodes. After being sterilized with alcohol, they were inserted perpendicularly in the midline of the upper surface of the right thigh to a depth of approximately 11 millimeters, usually about two inches apart. The lower electrode generally was about two inches above the patella. No noteworthy discomfort results from the presence of these very fine wires. As a rule, they can be withdrawn without bleeding. Contractions in the vastus femoris, particularly the medial portion, were recorded quantitatively in electrical terms. This can now be accomplished without recourse to photography, conveniently for medical purposes, by use of the Integrating Myovoltmeter.[5] The action-potentials are amplified (within a frequency range of 20–4000), rectified and averaged in voltage at intervals of time. Two minute intervals are employed in the present investigation.

The first recording was made before the subjects received any technical instruction in relaxation, the second 10 to 12 weeks later, following seven periods of training in the lying posture. (There had been also three lectures.) This was their first experience at recording. Instruction by methods described previously was limited to the chief muscle groups of the limbs. The subjects generally reported that they practiced 30 to 50 minutes daily, but with omissions.

In figure 1 is shown the graph for an individual (E) showing microvoltages higher than most of the others before training. The curve (unbroken line) begins with a microvoltage averaging above 6 during the first two minutes of recording while reading, but descends to about 1.5 during

the second two minutes, following an irregular course mostly from 0.5 to 1.5 during the remaining 26 minutes. After training, it is evident that the muscle tested is on the whole very much more relaxed during the 30 minute period, for the tracing (broken line) runs throughout 28 minutes below 0.5 microvolt.
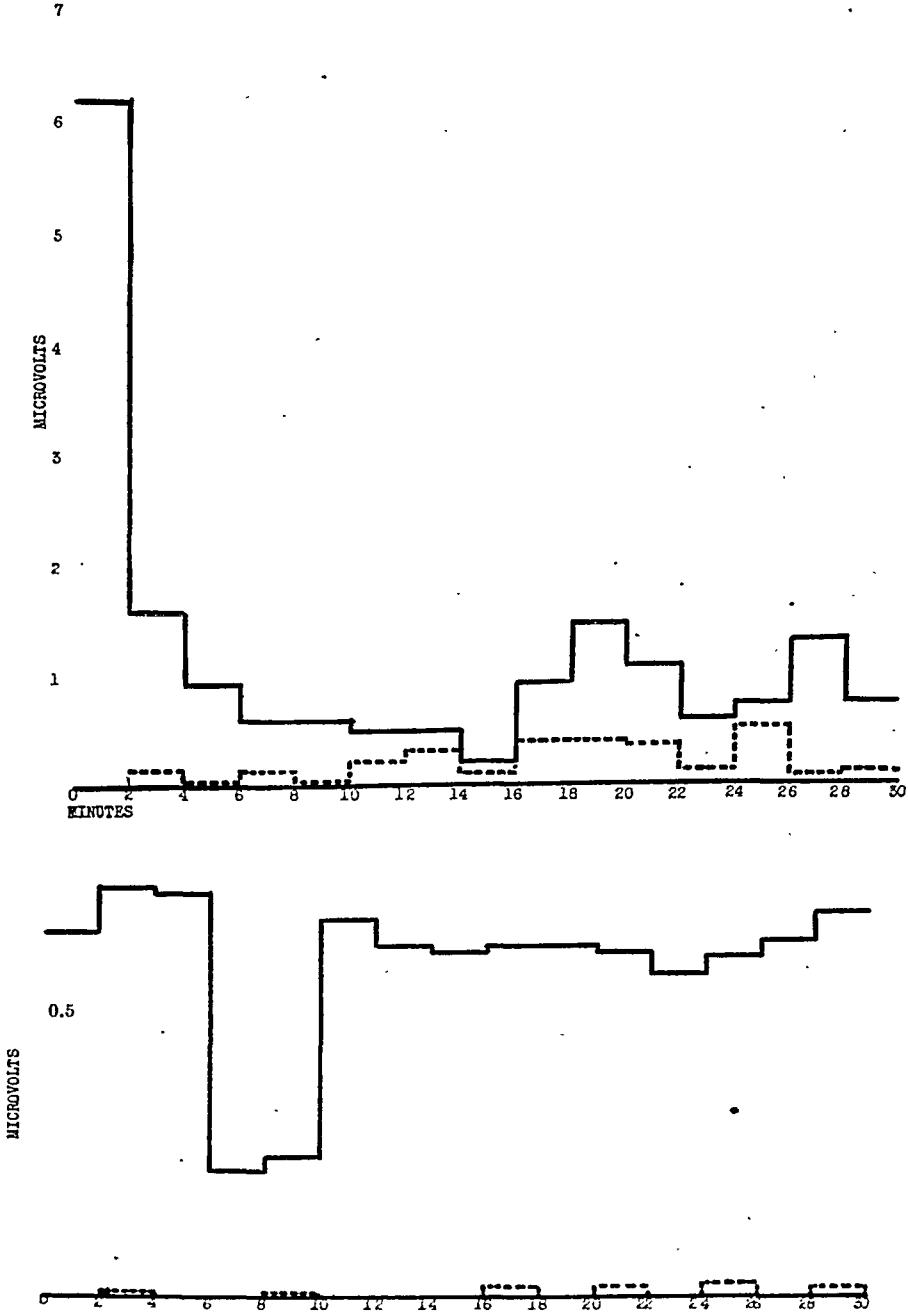
FIG. 1. (*Above*) Graphs for Subject E before training (unbroken line) and after (broken line).
FIG. 2. (*Below*) Graphs for Subject D before training (unbroken line) and after (broken line).

In figure 2 appears the graph for the individual (D) showing the lowest microvoltages before training. It runs fairly horizontally between 0.6 and 0.8 microvolt, excepting from min. 6–10, during which it is between 0.2 and 0.3 microvolt. Low as are these initial values, there is nevertheless a striking fall in the curve after training; for then the values are approximately
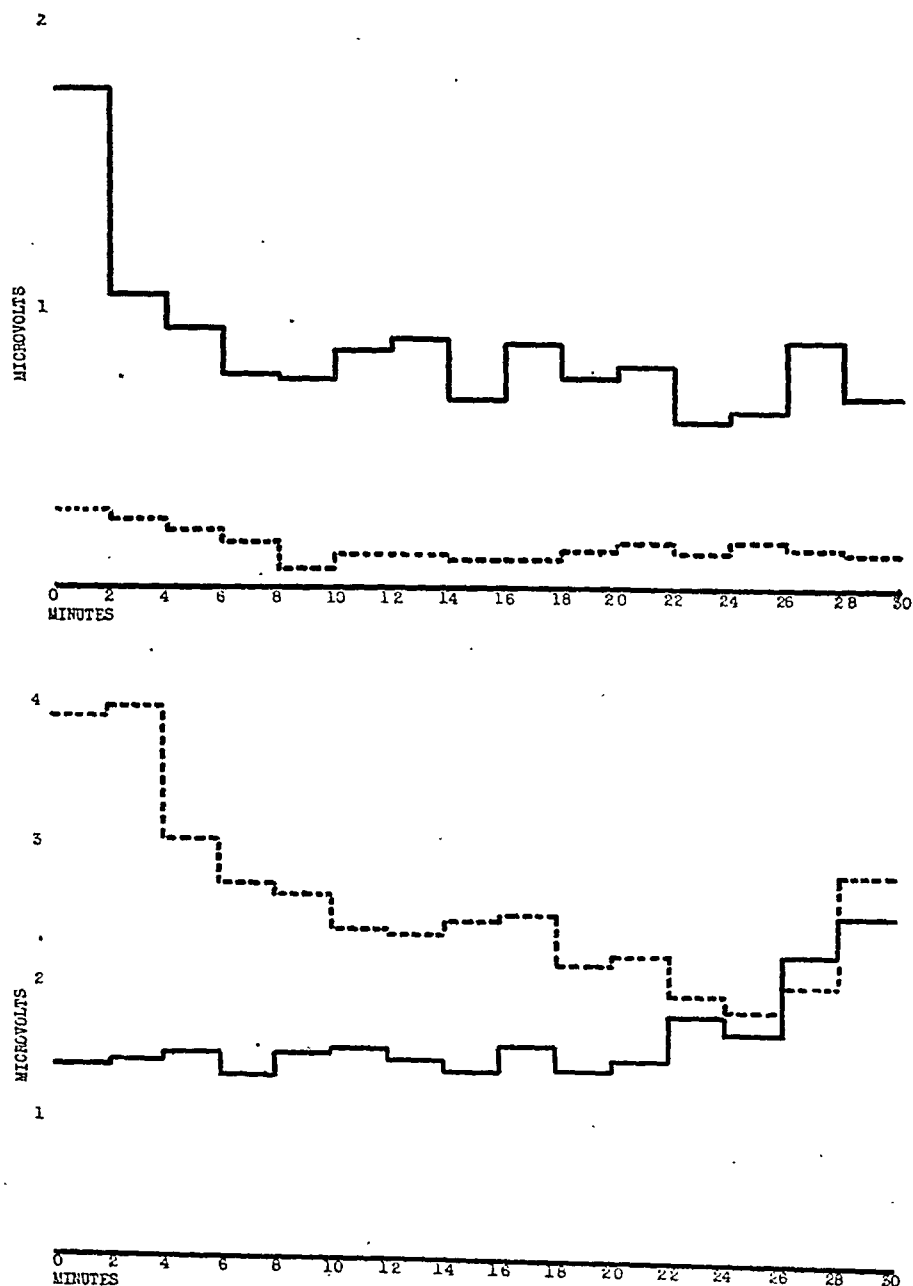
FIG. 3. (*Above*) Composite graphs for seven subjects before training (unbroken line) and after (broken line).

FIG. 4. (*Below*) Composite graphs for 10 subjects employed as controls before (unbroken line) and after (broken line) an interval of time approximately equal to that of the training course.

zero. The differences between them and zero are negligible, for they lie within the errors of the instrument. Declines similar to those shown for subjects E and D appear in the curves for the other subjects after training.

Before training, the composite curve for all the subjects, shown in figure 3, extends at 0–2 min. approximately at 1.8 microvolts; thereafter it lies mostly between 0.3 and 1.05 microvolts, nowhere falling below 0.3. After training it shows fewer irregularities, extending throughout its course below 0.25 microvolt.

TABLE I

Averaged Contraction Microvoltage for the 30 Minute Period of Test

Subject	Tests		Subject	Control Tests	
	Before Training	After Training		First Record	Second Record
A	.63	.08	1	3.01	1.17
B	.66	.30	2	1.83	.25
C	.68	.08	3	1.23	.47
D	.61	.08	4	1.48	.53
E	1.20	.18	5	.98	1.44
F	1.21	.30	6	1.93	3.75
G	.85	.08	7	.25	5.62
Aver. of All	.83	.15	8	2.04	5.92
			9	1.34	6.26
			10	1.78	.35
			Aver. of All	1.58	2.57

Table 1 shows (first three columns) the microvoltages averaged for the entire 30 minute period, before and after training. As judged by these averaged electrical measurements of tonus or contraction in the right quadriceps femoris muscles, as well as by the curves, the individual was more relaxed after training than before training.

The foregoing evidence, however, is not complete proof that the increase in relaxation was the result of training. It is necessary to run control tests under similar conditions with other normal individuals and a similar interval of time between two recordings, but with no training. This has been done in ten instances, six women and four men, ranging in age from 23 to 61 years.

In only four out of these 10 instances do reductions in contraction voltages occur on the second reading, affording graphs entirely similar in appearance to those of the preceding figures. Perhaps these individuals became adapted to the conditions of test, showing a certain increased relaxation while reading. However, in four other subjects precisely the opposite relationship holds; the second set of readings runs considerably above the first. In the two remaining individuals of this control group, the broken and unbroken lines cross each other. In one of them the second recording on the whole is the more irregular and reaches levels over five times the higher; in the other, the second recording is much higher for the first four minutes, but much

lower for the rest of the period. Figure 4 contains the composite control records for the first and second recordings. On the whole the second recording proves distinctly higher than the first, the reverse of what occurred in the test subjects after training (figure 3).

In the last three columns of table 1 are presented the averaged microvoltages for the control group. These averages show no reduction in contraction potentials in the control group upon the second recording. If the control group shows negative results, both in the averages and in the curves considered, it seems safe to conclude that the increased relaxation found in the test subjects was due to the training course.

During the present investigation, the subjects were always measured while reading in an unsupported, upright position, not lying on their backs with eyes closed as they were during the training period. Under these conditions, since the muscular region measured showed greater relaxation after training, the effects of training evidently were carried over from the lying posture, in which training was given, to the sitting posture in which the tests were made. The carry-over or "conditioning" which has been frequently noted in clinical practice of relaxation for therapeutic or preventive purposes can to this extent be confirmed.

Another matter can be noted. During reading, each individual necessarily contracted various muscles from time to time, including the arm muscles to hold the periodical, the back muscles to sit up, the neck muscles to keep the head erect, the eye muscles to see the words and to follow the lines and doubtless certain other muscles as well. However, the vastus femoris muscles evidently do not fall into the category of muscles indispensable to the act of reading in the sitting posture. They can be relaxed while such an act goes on. Relaxation during activity is known in the physiological literature as "differential relaxation." The present results are reminiscent of certain tests made on university students while reading.[6] No training in relaxation was given, but the students for the most part became more relaxed, as measured by a decline in the knee-jerk, as the hour of test wore on. This apparently illustrated a process of adaptation.[7] Such adaptation, we find, may arise automatically, as in the students mentioned, or may be pedagogically cultivated, as in the present group of subjects.

SUMMARY AND CONCLUSIONS

1. Action-potentials were measured in seven "normal" subjects before and after seven hour periods of technical training in physiological relaxation. The interval between the two sets of measurements was about 10 to 12 weeks. Electrodes were inserted in the right quadriceps femoris muscle region, while the right foot hung freely. Throughout each period, the subject read a periodical.

2. The action-potential curves and the average values were markedly reduced following the training.

3. No such reductions were found in most of the control tests under similar conditions with other subjects who received no training.

4. It is confirmed again that the results of technical training in relaxation are quantitatively demonstrable.

5. All measurements were made in the sitting posture, while reading. Evidently, training procedures administered in the lying posture can recondition the neuromuscular state in other postures. Training in general relaxation can contribute toward differential relaxation.

BIBLIOGRAPHY

1. WAKEFIELD, E. G.: Etiologic considerations of functional disorders of the colon, Proc. Staff Meet. Mayo Clin., 1937, xii, 193.
2. JACOBSON, E.: Electrical measurements concerning muscular contraction (tonus) and the cultivation of relaxation in man. The effects of daily rests without training to relax on muscular tonus, Am. Jr. Psychol., 1942, lv, 248.
3. JACOBSON, E.: Treatment of nervous irritability and excitement, Ill. Med. Jr., 1920.
4. JACOBSON, E.: Progressive relaxation, Rev. Ed., 1938, Univ. of Chicago Press, Chicago.
5. JACOBSON, E.: An integrating voltmeter for the study of nerve and muscle potentials, Rev. Sci. Instr., 1940, xi, 415–418.
6. JACOBSON, E.: Differential relaxation during reading, writing and other activities as tested by the knee-jerk, Am. Jr. Physiol., 1928, cxxxvi, 675.
7. Editorial: Differential relaxation, Jr. Am. Med. Assoc., 1928, xci, 1465.

PERFORATION OF THE INTERVENTRICULAR SEPTUM FOLLOWING INFARCTION; INTRAVITAM DIAGNOSIS

REPORT OF A CASE AND SURVEY OF THE LITERATURE *

By Manuel L. Weber, M.D., *San Francisco, California*

Despite the ease with which a correct diagnosis of rupture of the interventricular septum, occurring in the course of cardiac infarction following coronary thrombosis, could be made during life, if the characteristic criteria of the diagnosis of this complication are borne in mind, only in very rare instances has the condition been recognized clinically, as indicated by the meager reports in the literature. For almost a century, from 1845, when Latham [1] first described rupture of the infarcted septum of the heart, to Sager's [2] comprehensive survey of the subject in 1934, only 18 instances of this type of septal perforation were recorded in the literature, despite the seemingly increasing incidence of coronary thrombosis throughout the world. Through a careful search of the literature, both domestic and foreign, to 1942, I was able to collect 16 additional cases, bringing the total number on record to 33, which testifies to the rarity of the condition. Surprisingly small as the number of such cases found at the autopsy table seems to be, the number correctly diagnosed during life and subsequently confirmed by necropsy is much smaller, there being only five. The purpose of this report is to review the subject completely up to date and to present another case of perforation of an infarcted septum recognized antemortem.

CASE REPORT

U. U., a World War I veteran, aged 46, had always been in good health except for frequent "colds" during the preceding two or three years. He was active as an automobile salesman and had led a normal social life. About three months prior to the onset of his last illness, during one of his "colds," he was examined by a physician and was told that his blood pressure was somewhat high and that his pulse was rapid. He returned for reëxamination two weeks after the "cold" cleared up and was assured that there was nothing wrong with his heart, whereupon he returned to work. On September 24, 1941, he was awakened during the early hours of the morning with moderately severe substernal pain, which lasted about one hour and a half, and which was accompanied by a sense of oppression and dyspnea. However, the pain gradually subsided and, although the patient felt somewhat tired in the morning, he went to work as usual and continued at it for three days. On the third day, shortly after supper, he was suddenly seized with severe, "excruciating" pain in the midsternal and epigastric regions with a projected ache in both arms. "I felt like some-

one was pulling a bundle of nerves." The pain persisted all night, fluctuating in severity. There was no nausea or vomiting but the patient perspired freely and became rather apprehensive and dyspneic.

He first attended the outpatient clinic on September 29, where he was examined and an electrocardiogram and a roentgenogram of the chest (figure 1) were taken. The record of the outpatient examination failed to mention any pathological cardiac signs. The heart was not enlarged. The blood pressure was 150 mm. Hg systolic and 100 mm. diastolic. The rhythm was regular. The rate was 92. No murmurs were recorded. A roentgenogram of the chest revealed a small area of calcification near the base of the right lung; otherwise it was normal. The patient did not desire to
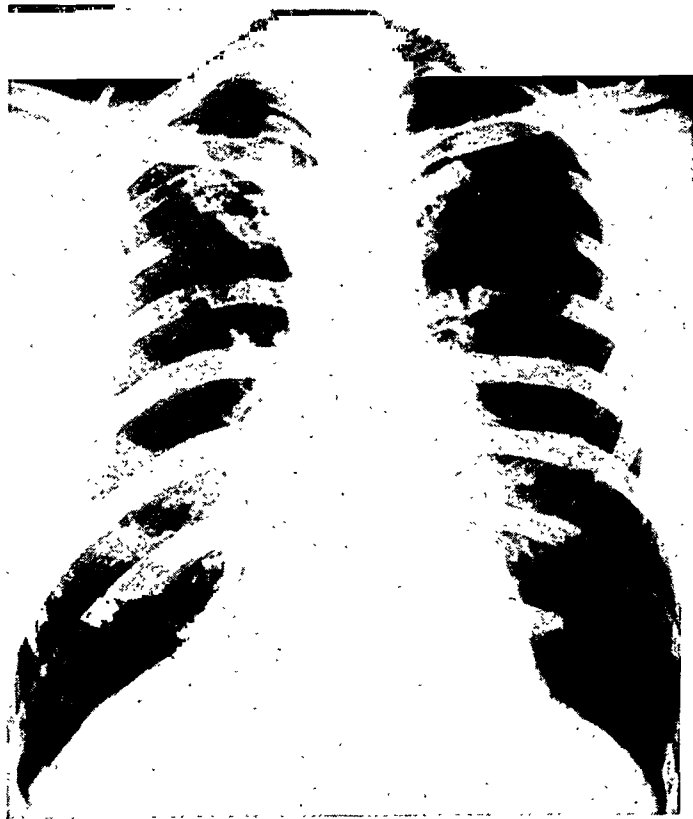
·FIG. 1.   Roentgenogram of chest taken September 29, 1941, showing normal· cardiac shadow.

enter the hospital then, but returned to his home in Sacramento (100 miles by auto). While there he continued having thoracic pain and dyspnea. He was finally admitted to the hospital on October 3, 1941, nine days after he suffered the first attack.

Physical Examination.   When examined by me on October 3, the patient was sitting in a semirecumbent position. He was slightly cyanotic, very apprehensive and restless, pointing toward the chest to indicate pain. He was moderately dyspneic. There was slight distention of the external jugular veins. The liver edge was palpated 4 cm. below the costal margin and was tender to pressure. There was no peripheral edema.

The heart did not appear to be enlarged to percussion. There was a very loud, rough systolic murmur audible over the entire precordial area, maximal to the left of the sternum in the fourth and fifth interspaces. The murmur was also audible at the left subscapular region. There was a palpable systolic thrill over the ensiform area

and in the same locality where the murmur was maximal. There was no diastolic murmur at any point. The pulmonic second sound was louder than the second aortic. The rhythm was regular. The cardiac rate was 118, and the blood pressure was 110 mm. Hg systolic and 90 mm. diastolic. When he was first seen, no râles were made out in the chest but within a few days the patient developed numerous crackling râles in the right chest from the sixth rib down. Diminished breath sounds appeared over the bases.

Laboratory Findings. Several urinalyses were done, all of which revealed variable amounts of albumin ranging between one plus and a trace. There were a few hyaline casts. The total leukocyte count of the blood was 13,900 with 67 per cent polymorphonuclears. The erythrocyte sedimentation index was 28 mm. per hour by

FIG. 2. Roentgenogram taken October 11, 1941, showing cardiac enlargement and passive congestion through the lungs.

the Cutler method. On October 5 the temperature rose to 101° F., but from then on it was somewhat subnormal. The arm-to-tongue circulation time performed with decholin was 30 seconds. The venous pressure by the direct method was elevated to 16 cm. of water. Two days before his death the urea nitrogen was 68.1 and creatinine 2.7 mg. per 100 c.c. of blood. The Wassermann reaction was negative. The electrocardiogram (figure 3) was repeated on October 13 and showed a deviation in the main electrical axis to the right and changes in the T-waves in all leads, characteristic of the evolutionary pattern of an acute cardiac infarction. Bedside roentgenogram of the chest (figure 2) was repeated on October 11. Allowing for a certain amount of distortion due to the position in which the roentgenogram was taken, it was nevertheless apparent that compared with the previous film the heart was enlarged in size and the hilus shadows had become more prominent, both in density and size, apparently because of passive congestion.

Course of the Disease. Throughout his stay in the hospital the patient's course was progressively downward. He was constantly dyspneic and orthopneic. When placed in an oxygen tent he became "panicky" and asked to be removed. On October 9 he began to complain of "pins and needles" in the sole of the left foot and in the toes. He could not tolerate the weight of the covers. Both lower extremities were cold and gray-cyanotic, the left more so than the right and up to a higher level. "Beer spots" appeared on both feet. The pulse of the main arterial vessels of the feet
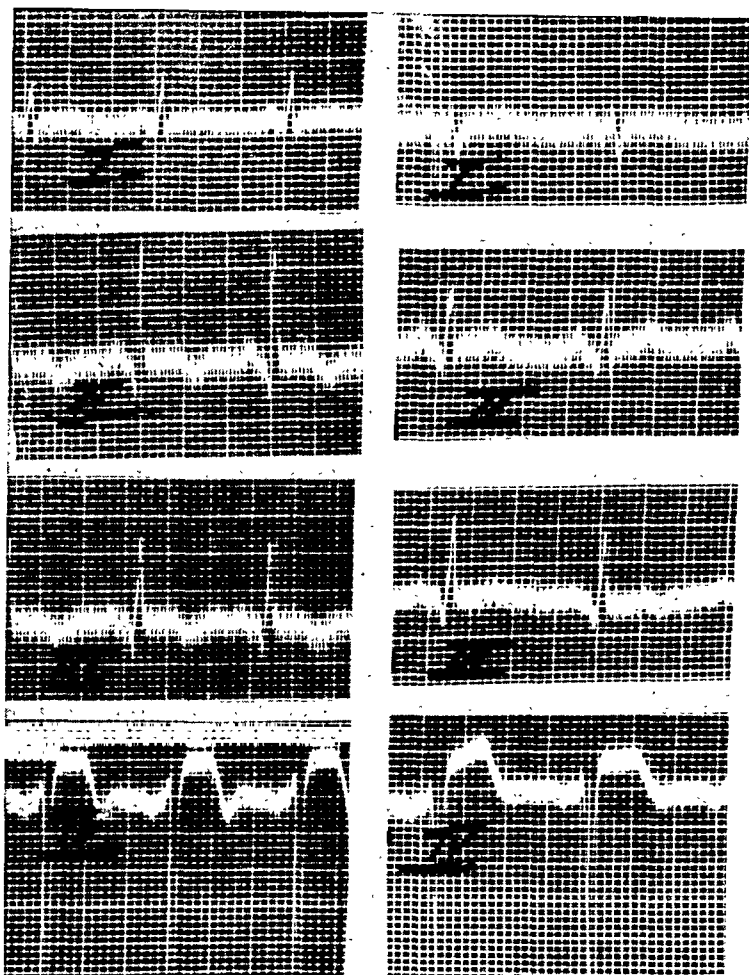
Fig. 3. Initial and final electrocardiograms. (a) 9/29/31—Leads II and III show presence of prominent Q-waves, negative T_2 and T_3. IVF shows small R, elevated S-T, and negative T. Normal axis deviation. (b) 10/13/41—Diphasic T_1, prominent Q_3. IVF— Large Q, elevated S-T and negative T. Right axis deviation.

was absent but the popliteal arteries pulsated strongly. Two days later both hands became deeply cyanotic and cold, although there was a good pulse in the radials. Early dry gangrene of all the toes of the left foot made its appearance toward the end. He developed slight pitting edema of both feet. Dullness and râles at the bases of both lungs became more marked. While at first the patient was irritable and restless, toward the end he became indifferent, only complaining of pain in the chest and feet when directly questioned. The cardiac signs, including the murmur and thrill, persisted unchanged until death. The patient died in shock on October 15, 1941, twenty days after the initial attack.

Antemortem Diagnosis. The diagnosis of cardiac infarction following coronary thrombosis was practically certain from the day of the patient's admission to the hospital on the basis of the history and electrocardiographic findings. An additional diagnosis of rupture of the interventricular septum was entered for reasons to be discussed later. In the course of the illness there appeared evidence of right heart

FIG. 4. Anterior view of the heart looking into the left ventricle, showing aneurysm of septum and perforation.

failure in addition to left heart failure with which the patient came to the hospital. The peripheral vascular symptoms might be regarded as resulting from multiple emboli, were it not for the unusual involvement of all four extremities in the absence of embolism to other organs such as the brain, kidneys or spleen. Fishberg [8] pointed out that shock may, in rare instances, cause peripheral circulatory failure of such a degree as to result in peripheral symmetrical gangrene. Unfortunately, the source of the beginning gangrene in this case was not found at postmortem examination, but

from its symmetry—all four extremities—one can surmise that it was not due to em-
bolization, but rather to peripheral circulatory failure caused by weak heart action.

    Clinical Diagnosis. (1) Massive cardiac infarction with perforation of the inter-
ventricular septum. (2) Peripheral circulatory failure.

FIG. 5. View of the heart looking into the right ventricle, showing perforation,
communicating with left ventricle.

    Postmortem Examination. The fixed heart was examined by Dr. Eichorn,
University of California Hospital, who reported as follows:

    Gross Description. The specimen was a fixed heart and part of the aorta cut open
to expose the chambers. The organ weighed 454 grams. There was infarction of the
lower half of the interventricular septum and the immediately adjacent anterior
apical portions of the ventricles. · The infarcted half of the septum bulged into the
right ventricular chamber producing an aneurysmal dilatation in the lower part of the

left chamber about 4 cm. in diameter. In the anterior portion of this dilatation there was a rupture of the septum 1 by 2 by 2.3 cm. in size at a point 5.5 cm. from the apex. This established communication between the right and left chambers. No massive mural thrombi were present, although there was thrombotic material attached to the trabeculae carneae at the apex. The epicardium was smooth.

The left ventricle measured 1.8 cm. in its thickest part and 0.5 cm. at the apex. The right ventricle measured 0.7 cm. in its thickest part and 0.15 cm. close to the septal rupture. The coronary arteries showed atherosclerotic thickening.
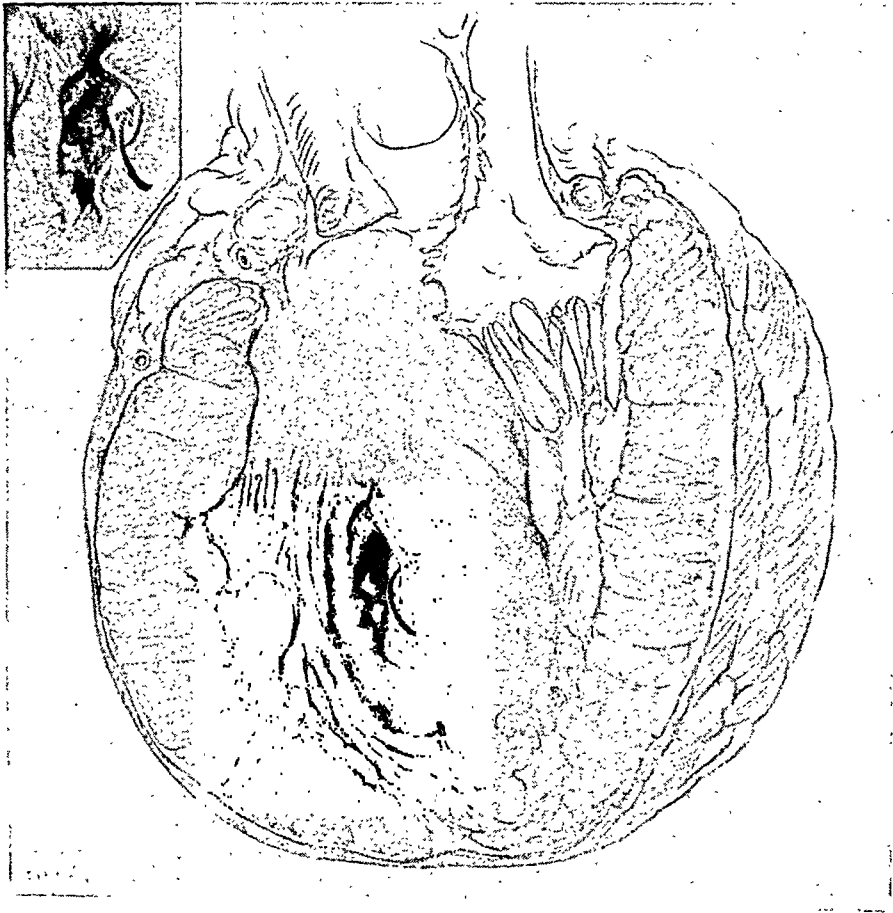
FIG. 6. Schematic drawing of the heart looking into the left ventricle; in the left upper corner a miniature drawing showing the opening from the right ventricle.

The valves grossly were not remarkable and except for the small thrombotic masses at the apex the endocardium was smooth.

Microscopic Description. The myocardium was hypertrophied and in the apical sections of the ventricles and septum the muscle was infarcted. Here the endocardium bore a mass of thrombus which showed early organization. The epicardial surface bore considerable fat which was increased in cellularity. There was no exudation on the epicardial surface. Scattered groups of small round cells occurred immediately beneath the epicardium in all of the sections. The coronary arteries showed considerable atheromatous thickening which was most marked in the anterior descending branch. This vessel had a crescentic lumen with dilation approximately ⅓ the combined thicknesses of the walls. There was much lipoid accumulation and fatty acid deposition beneath the thickened intima.

Anatomical Diagnosis. I. Arteriosclerotic heart disease with: A. Infarction of the epicardial portions of the right and left ventricles and interventricular septum. B. Aneurysmal dilatation and rupture of the interventricular septum anteriorly into the right ventricle at the apex.

REVIEW OF THE LITERATURE FROM 1924 TO THIS DATE

Kepler, Berkman and Barnes [4] reported a case of a man, aged 60, who was taken ill with severe substernal pain projected to the wrists. There was a marked systolic murmur over the entire precordium with its point of maximal intensity in the fourth and fifth interspaces and a sharp thrill to the left of the sternum. He went into a state simulating shock, characterized by a rapid fall in blood pressure, cyanosis and dyspnea. At necropsy there was an acute infarction of the apex, anterior portion of the left ventricle and of the adjacent interventricular septum, the infarction extending two-thirds of the distance from the apex to the base. In the lower part of the septum there was an irregular rent about 1 by ½ cm.

The patient of Master and Jaffe [5] was a woman of 65, who had had hypertension for at least four years. She was awakened from sleep experiencing a sensation of nausea. A few days later she collapsed while trying to get out of bed. She was dyspneic, cyanotic and perspired profusely. Her blood pressure dropped. There was a loud systolic murmur at the apex. There was no evidence of congestive failure. The electrocardiogram was characteristic of a coronary occlusion involving the posterior wall of the left ventricle. She died 11 days after being taken ill. Postmortem examination: Acute thrombosis of the posterior descending branch of the right coronary artery with myomalacia and pinpoint perforation of the posterior portion of the interventricular septum at the apex. The left anterior descending and circumflex arteries were narrowed. General arteriosclerosis was marked.

The case observed by R. Nadler [6] was a woman of 42, an inmate of an institution for the insane, who complained of dizziness, vomiting, cramp-like pain in the stomach and gall-bladder region. The heart was enlarged. There was a loud systolic murmur over the entire precordium. The blood pressure was 145 mm. Hg systolic and 110 mm. diastolic. She died the following day. Postmortem examination revealed a diffuse softening of the anterior wall of the left ventricle. Five centimeters above the apex there was a perforation of the septum. There was generalized coronary sclerosis and small thrombi in the left circumflex coronary artery.

Mahrburg's [7] patient was a man of 55 in apparent good health who had a sudden attack of severe chest pain radiating into the arms. He became weak and dyspneic. The heart was enlarged. There was a systolic murmur over the entire heart, best heard over the apex, and a systolic thrill. The blood pressure was 85 mm. Hg systolic and 8 mm. diastolic. The liver was enlarged and painful to pressure. One month later he developed a complete heart block and died. At necropsy the heart weighed 400 gm. The orifices

of the coronaries were free. There was marked thickening of the arterial wall of the left descending coronary and narrowing of its lumen for a distance of 2.5 cm. Four centimeters above the apex there was a defect in the septum in the form of a deep indentation, on the bottom of which there were four small openings communicating between the left and right ventricles. This case is distinct from the others in the reviewed series in that the septal defect caused the development of a complete block by interrupting the auriculoventricular pathway of impulses.

The two cases described by Bickel and Mozer [8] differ in several respects, the first being "silent" and the other having marked symptoms.

Case 1. A man of 87 enjoyed perfect health until 15 days prior to admission when he began to complain of weakness and loss of appetite. He developed a cough and became dyspneic. At no time did he have the least thoracic pain. There was no cyanosis and no edema. His respiration was of the Cheyne-Stokes' type. The heart was normal in size to percussion. The apical thrust was imperceptible. The sounds were feeble. There were no murmurs and no thrills. The blood pressure was 150 mm. Hg systolic and 70 mm. diastolic. There were signs of bronchopneumonia. The patient was disoriented and restless. During the five days in the hospital no new symptoms were apparent. Weakness rapidly increased. His blood pressure dropped gradually and he died in semicoma. Postmortem examination revealed an enlarged heart. The apex of the left ventricle was thinned out to 5 mm. forming an aneurysm. There was an oval opening 2 by ½ cm. in the septum at the level of its attachment to the posterior wall of the myocardium, permitting a large communication between the two ventricular cavities. The left coronary artery was completely obstructed by a thrombus at the level of its descending branch, 2 cm. from its origin. Another thrombus incompletely organized occupied the right coronary artery at the level where it curves to enter into the posterior ventricular groove.

Case 2. A man, aged 60, was admitted to the hospital in a state of weakness and intense dyspnea. Three weeks previously, he had developed extremely violent retrosternal pain radiating into both arms. The pain subsided somewhat but the dyspnea progressed throughout the subsequent days. His extremities were cold and cyanotic. The heart was slightly enlarged. There was a harsh systolic murmur over the entire precordium and an intense systolic thrill below the apex. The heart sounds were feeble. The blood pressure was 70 mm. Hg systolic and 50 mm. diastolic. There were râles of all sizes over both lungs. The liver was enlarged and painful to palpation. He died the day after admission. Postmortem examination disclosed a markedly enlarged heart. The valves were normal and soft, except the aortic valve which was moderately sclerosed. The left ventricle was thinned out to 3 mm. near the level of the apex. The interventricular septum was greatly thinned out in the lower ⅓ and was necrosed in the center. There was an oval opening communicating between both ventricular cavities. The left anterior and the right circumflex coronary arteries contained several atheromatous plaques. The descending branch of the left coronary was obstructed 5 cm. below its origin by thrombosis.

Huber [9] in the same year presented two cases of rupture of an infarcted septum.

Case 1. A 70 year old woman was brought into the hospital in a moribund state. She appeared to have heart trouble but no findings are given. Postmortem examination revealed a "rent" 3 cm. long in the interventricular septum, 4.5 cm. above the apex. There was thrombotic closure of the descending branch of the left coronary artery and marked narrowing of the lumen of the right coronary artery.

TABLE I

Cases of Perforated Interventricular Septum Reported from 1924 to Date

No.	Year in Which Reported	Author	Sex of Patient	Age	Presence of Murmur and Thrill	EKG Findings	Site of Perforations	Size, Forms and Number of Perforations	State of Coronary Arteries	Period of Survival Following Perforations	Recognized Ante-Mortem
1–18	1934	Reviewed by Sager	—	—	—	—	—	—	—	—	—
19	1935	Kepler et al.	M	60	Murmur and thrill	?	Lower part	1 × 1½ cm.	?	?	No
20	1935	Master and Jaffe	F	65	Murmur	Post. infarction	Post. part near apex	Pinpoint	Thrombosis of rt. cor. art. Narrowing of lt. descending and circumflex	11 days	Yes
21	1935	R. Nadler	F	42	Murmur	?	5 cm. above apex	?	Thrombosis of lt. circumflex	2 days	No
22	1935	Mahrburg	M	55	Murmur and thrill	Complete block	4 cm. above apex	4 small openings	Narrowing of lt. descending	30 days	No
23	1935	Bickel and Mozer	M	87	None	?	Level of attachment of septum to the post. wall of myocardium	2 × ½ cm.	Complete thrombosis of lt. cor.; incomplete thrombosis of rt. coronary	20 days	No
24	1935	Bickel and Mozer	M	60	Murmur and thrill	?	Lower third	?	Thrombosis of lt. descending. Atheromatous plaques in lt. anterior and rt. circumflex	2 days	No
25	1935	Huber	F	70	No findings given	—	4.5 cm. above apex	Rent 3 cm. long	Thrombosis lt. descending; marked narrowing of rt. cor.	1 day	No
26	1935	Huber	M	66	Systolic and diastolic murmur over all valves	—	Inner portion	2.5 × 1.6 cm.	Near thrombosis of lt. descending	21 days	No

TABLE I—(*Continued*)

No.	Year in Which Reported	Author	Sex of Patient	Age	Presence of Murmur and Thrill	EKG Findings	Site of Perforations	Size, Forms and Number of Perforations	State of Coronary Arteries	Period of Survival Following Perforations	Recognized Ante-Mortem
27	1936	Gross and Schwartz	M	57	Murmur and thrill	R.A.D.	Central portion	Several cm.	Lt. circumflex completely occluded; atheroma of rt. cor.	5½ mo.	No
28	1936	Stern	M	59	Murmur	R.B.B.B.	5 cm. from the apex	Admitting middle finger	Occlusion of descending branch rt. cor.	1 day	No
29	1937	Stanley	F	61	Murmur and thrill	Cardiac infarction	5 cm. from the apex	2 openings 12 mm. and 3 mm.	Rt. coronary almost completely occluded 2 cm. from orifice. Lt. cor. contained calcified plaques	8 months	Yes
30	1937	Kogan	F	52	Murmur	Anterior cardiac infarction	Lower part	Oblong slit	Lt. descending occluded. Rt. cor. contained small plaques	?	No
31	1937	Kogan	M	67	Murmur	Posterior cardiac infarction	Central part	2 cm.	Lt. circumflex cor. greatly narrowed. Other coronaries narrowed	?	No
32	1939	Scott and Garvin	M	56	Murmur and thrill	?	6 cm. from the apex	Funnel shaped hole	Rt. posterior descending occluded. Arteriosclerosis of other coronaries	20 days	No
33	1941	Bayley and Fader	M	47	Murmur and thrill	Cardiac infarction R.A.D.	Basal region	3 openings	Marked narrowing of first part of rt. coronary. Moderate narrowing of lt. cor.	8 weeks	Yes
34	1942	Moolten	M	57	Murmur and thrill	Acute cardiac infarction	Central part	2 openings	Lt. descending markedly narrowed. Rt. narrowed by small plaque	12 weeks	No
35	1942	Weber	M	46	Murmur and thrill	Cardiac infarction R.A.D.	Lower half	1 × 2 × 2.3 cm.	Atheromatous thickening; most marked anterior descending	2 weeks	Yes

Case 2. A man, aged 66, was an invalid for three years because of arterio-sclerosis, dizzy spells and dyspnea. On January 31, 1935, he suffered pain in the heart region with radiation down the left arm. He had daily attacks from that time on. The heart was found to be enlarged. There were audible systolic and diastolic murmurs over all valves, maximal over the mitral area. The blood pressure was 80 mm. Hg systolic and 60 mm. diastolic. He died three weeks following the first attack of thoracic pain. Postmortem examination showed normal valves. At the apex there was great thinning of the left ventricular wall with an aneurysmal bulging. The inner portion of the interventricular septum contained a defect 2.2 by 1.6 cm. which communicated between the left and right ventricles. The descending branch of the left coronary artery was nearly closed by an organized thrombus.

Gross and Schwartz,[10] in 1936, described a case of a man of 57 who was suffering from hypertensive heart disease with congestive failure. The first symptoms became evident in September 1929, when he suddenly became unconscious for one and one-half hours. He was cyanotic. His breathing was stertorous and blood trickled from the mouth. During the following three months he had five such episodes. He was admitted to the Montefiore Hospital in a state of severe congestive failure with enlargement of the heart, engorgement of the cervical veins, swollen liver, bilateral hydrothorax and slight dependent edema. His blood pressure was 184 mm. Hg systolic and 128 mm. diastolic. The electrocardiogram revealed right axis deviation and slurring of the QRS complexes. There was a prolonged systolic murmur audible over the entire precordium and base of the heart and a systolic thrill over the same area. He succumbed to lobar pneumonia two months after admission. On postmortem examination the apex was found to be thinned and there was considerable fibrous tissue replacing the myocardium. The entire lower half of the septal wall was replaced by fibrous tissue and in the central portion of the septum there was a circular defect measuring several centimeters in diameter. The right coronary arteries showed considerable atherosclerosis with calcification. The anterior descending artery had two branches, both revealing marked atherosclerosis with calcification. The lumina were narrowed by large yellowish-gray plaques. The left circumflex artery was completely occluded by a firm thrombus about 1 cm. from its origin.

Stern[11] attended a man of 59 who complained of dyspnea and substernal pain for three weeks. Three days prior to admission to the hospital he suffered sharp, cutting substernal pain, radiating to the epigastrium and associated with severe dyspnea. The heart was enlarged. The sounds were faint and there was a slight systolic murmur at the apex. The blood pressure was 120 mm. Hg systolic and 85 mm. diastolic. An electrocardiogram showed right bundle branch block. Six days later his dyspnea increased, and his breathing became of the Cheyne-Stokes' type. The heart sounds were irregular. A loud systolic murmur appeared at the apex. He died the same day. At necropsy the heart was greatly enlarged. There was an area of infarction on the lateral and posterior surfaces, measuring 9 by 7 cm. There was a rent in the septum 5 cm. from the apex of the right ventricle perforating into the left ventricle, of a size which easily admitted the middle finger. The aortic cusps were thickened and calcified. The right coronary artery was normal except for calcification in the first inch. Its descending branch, about 3 cm. below the parent vessel, was occluded by a partially organized adherent clot.

The case reported by Stanley[12] which was the third on record in which the correct diagnosis was made during life, was that of a woman, aged 61, who was awakened by upper epigastric pain radiating upward into both arms, which was followed by vomiting. The heart was not enlarged to percussion and no murmurs were heard. The blood pressure was 140 mm. Hg systolic and 86 mm. diastolic. She gradually improved but three days later, while on the bedpan, she was stricken with substernal pain and went into shock with sweating, cyanosis and dyspnea. At that time there was heard a loud harsh systolic murmur accompanied by a thrill in the

fourth interspace to the left of the sternum. The blood pressure was 100 mm. Hg systolic and 60 mm. diastolic. On the basis of the clinical picture and electrocardiogram a diagnosis of coronary thrombosis was made. The patient died eight months after the beginning of her illness in a state of increasing decompensation and with a right hemiplegia. The cardiac murmur persisted until death. At necropsy the findings of congestive failure were marked. The heart was slightly enlarged. The posterior wall of the left ventricle was thinned out to 3 or 4 mm. and bulged backward forming an aneurysm. The adjacent half of the septum was composed of firm scar tissue and through its center were two oval holes 12 and 3 mm. in diameter communicating between the two ventricular cavities. The lumen of the right coronary artery, about 2 cm. from the orifice, was almost completely obliterated by a calcified plaque. The remainder of the right coronary, as well as the left coronary arteries had a moderate number of hyaline and calcific plaques.

Kogan [18] (Russia) attended two patients with rupture of the septum as the result of cardiac infarction within the short space of nine months.

Case 1. A woman, aged 52, complained of attacks of oppression in the region of the heart, pain in the right arm and scapula. She was dyspneic and cyanotic. The heart was enlarged to percussion. The sounds were faint. Blood pressure was 180 mm. Hg systolic and 120 mm. diastolic. At times there was a systolic murmur at the apex. Eight days later she suffered an attack of severe thoracic pain. Her pulse rose to 130 and there appeared a loud systolic murmur, maximal over the lower sternum. The blood pressure dropped to 125 mm. Hg systolic and 95 mm. diastolic. There appeared evidence of right heart failure. An electrocardiogram revealed the pattern of infarction of the anterior aspect of the left ventricle. She died with symptoms of progressive heart failure, and the systolic murmur remained loud to the very end. At autopsy the heart was found to be enlarged. The wall of the left ventricle near the apex was much thinned out and presented an aneurysmal bulge. The lower anterior portion of the septum contained an oblong slit connecting the ventricular cavities. The left coronary artery in its beginning contained many atherosclerotic plaques narrowing its lumen. The descending left coronary was completely occluded by thrombus. The right coronary artery was patent although it also contained small yellow plaques.

Case 2. A man of 67 developed severe pain in the heart region radiating to the back. Four days later he complained of great weakness, frequent attacks of vomiting and abdominal distention. The heart was enlarged. The pulse was weak. The blood pressure was 88 mm. Hg systolic and 70 mm. diastolic. Phenomena of right heart failure were present. There was a loud harsh systolic murmur in the fourth and fifth intercostal spaces near the sternum to the left. An electrocardiogram showed posterior infarction. He died following progressive cardiac weakness. Postmortem examination revealed the heart to be enlarged. All cavities were dilated. The valves were normal. In the central portion of the septum there was a rent 2 cm. in diameter connecting both ventricular cavities. The posterior walls of the ventricles were soft and tore easily. The aorta contained many plaques. The lumen of both coronary arteries was narrowed. The circumflex branch of the left coronary was greatly narrowed by calcification. There were no thrombi present.

In March 1939 Scott and Garvin [14] described a rupture of an infarcted septum in a 56 year old man who was admitted to the psychopathic ward because of disorientation, delusions and hallucinations which he developed following an episode of dizziness and unconsciousness. Except that there was evidence of marked arteriosclerosis, general physical examination was essentially negative. The heart was normal and the blood pressure was 135 mm. Hg systolic and 90 mm. diastolic. About six weeks later the patient developed a high temperature, dyspnea and evidence of broncho-

pneumonia. At that time over the entire precordium there was heard a loud systolic murmur which was transmitted to the base of the heart and to the left axilla and was accompanied by a sharp thrill. The blood pressure dropped to 98 mm. Hg systolic and 60 mm. diastolic. He died 20 days after the onset of his acute illness. Postmortem examination revealed a large heart weighing 550 gm. There was an irregular, funnel-shaped hole in the anterior portion of the interventricular septum 6 cm. from the apex connecting the two cavities. The edges of the lesion consisted of necrotic muscle tissue. The coronary arteries all showed marked arteriosclerosis. The right posterior descending branch was occluded but no thrombus was present.

Bayley and Fader [15] in February 1941 reported the case of a man of 47, who had experienced a sudden burning pain behind the upper part of the sternum, radiating to the left shoulder and down the left arm. The pain subsided within two hours. A few days later he was examined by a physician and was assured that his heart was all right. His blood pressure was 160 mm. Hg systolic and 120 mm. diastolic. A second attack occurred one week later with pain in the left hypochondriac and epigastric regions associated with nausea, vomiting, weakness and dyspnea. A "leak in the heart" was diagnosed by a consultant. When admitted to the hospital two weeks later the heart was enlarged. A loud, rough murmur which lasted throughout systole and a pronounced thrill were found to the left of the sternum in the fourth and fifth interspaces. The liver was enlarged and tender. Dense mottling through both bases and in the region of the hilus of the lungs was seen in the roentgenogram which was interpreted as evidence of pulmonary edema. An electrocardiogram was characteristic of a cardiac infarction. Gradually, the phenomena of right heart failure made their appearance and the patient died eight weeks after admission. The precordial thrill and murmur remained unchanged throughout the illness. Postmortem examination revealed a moderately enlarged heart and an aneurysmal dilatation of the apex of the left ventricle. The thickness of the left ventricle at the base was 14 mm., but the aneurysmal sac was thinned out to 2 mm. In the basal region of the interventricular septum there were three openings which connected the two ventricular chambers. There was marked narrowing of the first part of the right coronary artery and moderate narrowing of the left coronary artery. No area of total occlusion was found.

Finally Moolten [16] in 1942 reported the case of a man, aged 57, who suffered an attack of severe precordial pain. Two weeks later he began to experience marked dyspnea. On physical examination, the heart was greatly enlarged, there was dependent edema, the liver was swollen, the cervical veins were engorged and there were signs of right-sided hydrothorax. The venous pressure by the direct method was 23.5 cm. of water. The electrocardiogram was characteristic of an acute myocardial infarction. A loud systolic murmur and a palpable thrill were present at the apex.

The patient lived 12 weeks. At necropsy, a double perforation of the central part of the interventricular septum was found. The descending branch of the left coronary artery was markedly narrowed by calcified atheroma. A small plaque of soft atheroma in the intima of the right coronary artery caused narrowing of the vessel. The perforation was not recognized antemortem.

COMMENTS AND CONCLUSIONS

Since the description by Rogers in 1879 of the clinical symptoms of perforation of the interventricular septum, the congenital form has been amply

studied, but very little attention has been accorded to the acquired forms. The immediate causes of spontaneous rupture of the septum, aside from the type under consideration here, are either traumatic or ulcerative. To the latter belong the rare instances of septal perforation due to an ulcerative endocarditis. The site of predilection of the perforation in the congenital form is in the upper membranous part of the septum where its thinness explains its particular vulnerability. The third variety of the acquired perforation, i.e., the one resulting from an ischemic massive necrosis following thrombosis or marked narrowing of one or more major branches of the coronary arteries, has its site of predilection in the lower muscular portion of the septum. This variety, which in the majority of cases has been discovered at necropsy, appears to be exceedingly rare, as one would judge from the poverty of published reports, but in reality is probably more common, many cases having been overlooked at postmortem examination due to very small perforations. There is no doubt, however, that the incidence of perforation of an infarcted septum is much lower than that of rupture of the heart following infarction.

. Mönckeberg [17] in a compilation of 39 cases of rupture of the heart by all causes found only three interventricular septum defects, a ratio of 1 to 13, and according to others, the ratio is even much lower. This fact is explained by the rich blood circulation with which the lower portion of the septum is endowed, since both major coronary arteries contribute to its supply, as demonstrated by Gross [18] by means of injection.

The common denominators for the diagnosis of a septal rupture of this variety are two: (1) coronary thrombosis followed by (2) the sudden appearance of a loud systolic murmur and palpable thrill. In all cases comprising this review, including our own, with the exception of the first case of Bickel and Mozer (which the authors relegated to the "silent type"), there was a loud systolic murmur, most frequently heard best to the left of the sternum in the fourth and fifth interspaces. The absence of the murmur in Bickel's case may have been due to weakness of cardiac contractions. This location is in contrast to that of the murmur found in the congenital form, which is usually higher over the heart. It has been stated by Sager and others that the intensity of the murmur and thrill depends on the size of the aperture, the smaller the opening, the louder the murmur and the rougher the thrill. This review does not bear out such a conclusion.

The electrocardiographic findings which accompany this complication, in the majority of instances, do not differ from those characteristic of other cases of cardiac infarction, and depend on whether the involvement is greater in the anterior or posterior portions of the heart—the Q_1T_1 or Q_3T_3 type. It has been particularly noted that auriculoventricular conduction defects are rare. In only one case did the patient develop a complete block. The absence of conduction interference is accounted for by the fact that only a few twigs of conduction fibers are present in the apical portion of the septum; thus, its destruction has no influence on the electrocardiogram. However, in the cases of Gross and Schwartz and of Bayley, as well as in my

own, as the illness progressed, there was a change in the axis from normal to deviation to the right. With the clinical evidence of increasing right heart failure, the change in the axis deviation indicates augmented strain on the right side of the heart, similar to cor pulmonale, a finding which may be of aid in arriving at a correct diagnosis.

It appears from all reports that the addition of rupture of the septum to the presence of cardiac infarction makes the prognosis much more grave, although on theoretical considerations the cardiac dynamics should not be greatly affected. The intraventricular tension in the left ventricle being considerably greater than that in the right, the flow of blood, in the presence of an acquired interventricular aperture, is in the direction from left to right; thus, cyanosis is not an outstanding feature. What makes the outlook worse is the fact that the rupture of the septum is prima facie evidence of massive infarction of the myocardium. The duration of survival after the appearance of the murmur varies from a few days to several months. The patient of Gross and Schwartz lived five and one-half months after the murmur appeared, long enough to develop congestive failure. Stanley's patient died eight months after the beginning of her illness.

The size of the perforation varies from a pinpoint to 6 cm. There is usually only one communication, but in a few cases there were two or more.

In all the cases reviewed there was either complete occlusion of one or more of the major coronary arteries or marked narrowing of their lumina. In the majority of cases the left coronary artery was the one most severely affected, a fact which is consistent with the greater frequency of infarction of the anterior wall of the left ventricle. Evidence of atherosclerosis of the right coronary artery was also present in most cases. It is the opinion of most observers that although perforation of the septum usually follows thrombosis of the left coronary which supplies two-thirds of the septum, actual perforation does not take place unless the right coronary is also severely sclerosed and thus becomes incapable of supplementing, by way of anastomosis, the deficiency of the anterior coronary vessels. As was shown with special clarity by Blumgart et al.[19] multiple occlusions and narrowings of both coronary arteries are usually found in cases of massive infarction.

The diagnosis of this complication, as stated above, should not be difficult in most cases. A wider dissemination of the knowledge of the symptomatology which occurs when rupture of the septum follows coronary thrombosis should result in the more frequent recognition of this condition during life. One condition which may lead to difficulty in differential diagnosis is a sudden tear of a papillary muscle in the left ventricle. In that case, however, the clinical condition would show a more spectacular change for the worse than in the case of septal rupture, as one would expect to find the cardiac dynamics affected to a greater degree. The heart would dilate more rapidly and the clinical and electrocardiographic aspects would point toward greater failure of the left heart than of the right heart. The presence of relative tricuspid insufficiency as the result of weakness of the right ventricle may

lead to confusion in explanation of the systolic murmur, but in that case the murmur would be loudest over the xiphoid region rather than to the left of the sternum, and usually no thrill would be present. The history, electrocardiographic changes sufficient to make a diagnosis of cardiac infarction, and a suddenly appearing loud systolic murmur and thrill to the left of the sternum in the fourth and fifth interspaces make the diagnosis of ruptured septum most plausible.

Summary

1. An up-to-date review of the literature on perforated septum following cardiac infarction is presented and an additional case, diagnosed before death, is described.

2. Comments on the clinicopathologic syndrome are made.

BIBLIOGRAPHY

1. LATHAM, P. M.: Lectures on subjects connected with clinical medicine comprising diseases of the heart, 1845, Longmans, Brown, Green & Longmans, London, vol. 2, p. 168.
2. SAGER, R. V.: Coronary thrombosis; perforation of the infarcted interventricular septum, Arch. Int. Med., 1934, liii, 140.
3. FISHBERG, A. M.: Heart failure, 4th Edition, 1940, Lea and Febiger, Philadelphia, p. 656.
4. KEPLER, E. J., BERKMAN, J. M., and BARNES, A. R.: Acute myocardial infarction with rupture of the septum, Proc. Staff Meet. Mayo Clin., 1935, x, 209.
5. MASTER, A. M., and JAFFE, H. L.: Acute coronary artery occlusion with perforation of the interventricular septum, Jr. Mt. Sinai Hosp., 1935, ii, 182.
6. NADLER, R.: Perforation of interventricular septum, Ztschr. f. Kreislaufforsch., 1935, xxvii, 689.
7. MAHRBURG, S.: Perforation of ventricular septum—chronic course, Frankfurt. Ztschr. f. Path., 1935, xlvii, 552.
8. BICKEL, G., and MOZER, J. J.: Perforating infarction of interventricular septum—two cases, Bull. et mém. Soc. méd. d. hôp. de Par., 1935, li, 1564.
9. HUBER, H.: Acquired defect of interventricular septum, Ztschr. f. Kreislaufforsch., 1935, xxvii, 825.
10. GROSS, H., and SCHWARTZ, S. P.: Acquired interventricular septal defect, Am. Heart Jr., 1936, xi, 626.
11. STERN, N. S.: Rupture of interventricular septum: case, Memphis Med. Jr., 1936, xi, 35.
12. STANLEY, D. F.: Acquired interventricular septum defect, Am. Heart Jr., 1937, xiv, 240.
13. KOGAN, M. B.: Clinics on perforated infarct of the interventricular septum, Klin. Med. (Russia), 1937, xv, 580.
14. SCOTT, R. W., and GARVIN, C. F.: Myocardial infarction with rupture of the septum, Am. Heart Jr., 1939, xvii, 375.
15. BAYLEY, R. H., and FADER, D. E.: Ante-mortem diagnosis of rupture of the interventricular septum as a result of myocardial infarction, Am. Heart Jr., 1941, xxi, 238.
16. MOOLTEN, S. E.: Prolonged survival after perforation of the infarcted interventricular septum in coronary arterial disease, Arch. Int. Med., 1942, lix, 108.
17. MÖNCKEBERG: Beiträge, Henke-Lubarsch, II, 1924. (Berlin.)
18. GROSS, L.: The blood supply of the heart in its anatomical and clinical aspects, 1921, Paul B. Hoeber, Inc., New York, p. 85.
19. BLUMGART, H. L., SCHLESINGER, M. J., and DAVIS, D.: Studies on the relation of the clinical manifestations of angina pectoris, coronary thrombosis and myocardial infarction to the pathological findings, Am. Heart Jr., 1940, xix, 1.

AMYLOIDOSIS COMPLICATING TUBERCULOSIS— DIAGNOSIS, PROGNOSIS AND TREATMENT.*

By Samuel Cohen, M.D., F.A.C:P., *Rochester, New York*

I. Introduction

The substance, amyloid, is now considered to be a complex protein, the exact chemical composition of which has not yet been definitely determined. The disease, secondary amyloidosis, is looked upon by most contemporary observers as a disturbance of protein metabolism.

More effective treatment of syphilis and a more prompt surgical attack on suppurative foci have undoubtedly reduced these two common conditions as potential sources of amyloidosis and have served to center attention on tuberculosis as the chief current cause of this complication. The lesson is obvious. Early and adequate control of precavitary tuberculosis will prevent amyloidosis. The earlier and effective use of collapse therapy measures in advanced cases will minimize the development of amyloidosis. When the complication appears the prognosis is affected adversely. The advanced case of amyloidosis is a well known clinical picture and of academic interest only.

Table I

Incidence as to Race, Sex and Age

	Race		Sex		Age at Death	
	White	Colored	Male	Female	Youngest	Oldest
Number..............	63	16	43	36	14	67
Per Cent.............	80	20	54	46	66% of cases in age group between 20–39 yrs.	

The recognition of amyloidosis in its relatively early stage is of more importance and should stimulate reconsideration of methods for possible control of the underlying tuberculous lesion. Finally, there is the problem of active therapy directed toward the amyloidosis itself.

Material: This report briefly considers some features concerning the diagnosis, prognosis and treatment of amyloidosis. The study is based on a review of 79 patients who died of tuberculosis complicated by amyloidosis. The series is composed of: (*a*) Fifty-three cases in which the diagnosis of amyloidosis was proved by necropsy examination during a six year period ending January 1942. A total of 143 autopsies was performed and the incidence of amyloidosis was 39 per cent. (*b*) Twenty-six patients who, during life, had clinical evidence of amyloidosis and 100 per cent absorption

of the congo red dye but in whom necropsies were not done. These patients were observed between January 1939 and January 1942.

II. Diagnosis

A. Clinical Features:

1. The distribution of the cases as regards race, sex and age is presented in table 1.

2. The type of the underlying lesion in these patients can be summarized briefly as follows:

a. *Pulmonary Tuberculosis:* Seventy-seven or 97.4 per cent had progressive disease of varying degree with cavitation in one or both lungs. Many had also extrapulmonary involvement, particularly of the larynx and intestines. Only two patients, or 2.6 per cent, had arrested disease at the time of death.

b. *Pleural Tuberculosis:* Fifteen patients, or 19 per cent had an empyema (tuberculous or mixed); 13 were intrapleural and two extrapleural. By contrast, 8 of 88 autopsied non-amyloid patients, or 9 per cent, had an empyema. Thus, twice as many patients with empyema developed amyloidosis.

c. *Major Surgical Operations:* Six patients had thoracoplasty operations, three extrapleural pneumothoraces, and one patient both procedures. Two of the group were definitely known to have amyloidosis at the time of operation. Both died shortly after thoracoplasty, one with uremia, the other with a nephrotic syndrome.

d. *Associated Non-Tuberculous Disease:* One patient had a recurrent osteomyelitis of 16 years' duration, and another carcinoma of the pharynx and tongue. These conditions may have contributed to the development of amyloidosis.

3. *Hypertension:* Eight cases, or 10 per cent, of the group had hypertension.

4. *Hepatomegaly:* The liver was enlarged on physical examination in 46 cases, or 58 per cent; in the remainder, the liver was not felt on admission and no follow up notes were available. No instance of jaundice was seen.

5. *Splenomegaly:* The spleen was definitely palpable in 18 cases, or 22 per cent; no enlargement was found despite frequent examinations in 36, or 45 per cent; the spleen was not palpable on admission in the rest of the group and subsequent notations were not made.

6. *Clinical Status at Death:*

1. Causes not related to amyloidosis—intermittent complications such as profuse terminal hemoptysis, meningitis, etc., which interrupted the evolution of amyloidosis .... 15 cases, or 19 per cent
2. Progressive asthenia and no edema .... 23 cases, or 29 per cent
3. Slight to moderate edema .... 12 cases, or 15 per cent
4. Anasarca (including ascites) .... 24 cases, or 30 per cent
5. Uremia .... 5 cases, or 6 per cent

Dependent edema of the extremities in some instances was recurrent and
not persistent.   Once ascites set in, however, it tended to be persistent and
the prognosis became graver.   A complicating terminal pneumococcic peri-
tonitis, seen frequently in non-amyloid nephrosis, did not occur in our series.

Amyloidosis is an insidious complication of tuberculosis.   The com-
monest clinical signs are hepatomegaly and edema.   Congestive heart failure
must be excluded.

B. Laboratory Data:

1. *Blood:*

(*a*) *Anemia:* Sixty-seven of the 79 cases, or 85 per cent, presented
anemia of varying degree.

(*b*) *Blood Chemistry:* Repeated determinations were usually made at
three to four month intervals and very rarely longer than six months.

(*a*) Plasma protein determinations done in 49 cases showed decreased
total protein and albumin in 53 per cent, hyperglobulinemia in 24
per cent, and a decreased or inverted A–G ratio in 63 per cent.

(*b*) In 10 out of 53 cases, or 19 per cent, the nitrogen values were above
normal.

(*c*) Fifty-two per cent of a group of 40 showed a hypercholesteremia.

These figures represent the average pattern.   Normal values may occur inter-
mittently.   The commonest laboratory findings in amyloidosis are decreased
plasma proteins, A–G ratio, and elevated blood cholesterol.

2. *Renal Function Tests and Urinary Findings:*

Two kidney function tests were repeated with other clinical and labora-
tory studies.

(*a*) The renal concentration test was done in 50 cases and poor con-
centration was noted in 41, or 85 per cent.

(*b*) The phenolsulfonphthalein intravenous excretion test was performed
in 38 cases and poor elimination of the dye was observed in 20, or
52 per cent.

We found the concentration test a better index of renal function in our amy-
loid cases.

Routine Examination of the Urine: A review of the urine examinations
in the 53 autopsied cases and in a control group of 88 autopsied tuberculous
cases who did not have amyloidosis (five of the latter had no urine examina-
tions so that the estimate is based on 83 cases) was undertaken.   The heat
and acetic acid test was uniformly used to detect albuminuria by which we
mean the presence of albumin of one plus or more in one or more specimens.
By casts we mean the presence of hyaline or granular casts (many, few,
occasional) in one or more samples of urine.   In the vast majority of in-
stances, the casts were hyaline only.

The very significant fact gleaned from table 2 is that 74 per cent of all the tuberculous patients who had proteinuria with casts were in the amyloid category. A checkup of the anatomical distribution of amyloidosis in the 53 cases revealed that 45, or 85 per cent, showed renal involvement. All of the 37 cases with albuminuria plus casts, or 82 per cent of the total affected kidneys, had amyloidosis. In four of the remaining eight cases minimal amyloid disease of the kidney was present; in three of these the urine was normal, whereas the fourth had albuminuria alone. Four other patients had moderate to marked renal amyloidosis. One patient had albuminuria, whereas three had negative findings and the time intervals between the last urine examination and dates of death were five and one-half months, five months and six weeks. It is possible that in at least two of these patients, study of the urine closer to death might have revealed positive findings.

TABLE II

Urinary Abnormalities in Autopsied Cases

Urinary Findings	Autopsied Amyloid Cases No.	Autopsied Non-Amyloid Cases No.	Total = 136 Cases	
			No.	%
Albumin only................	5	20	25	18.3
Casts only..................	0	2	2	1.4
Albumin + Casts.............	37	13	50	36.7
Negative Urine..............	11	48	59	43.3

Note: In the clinically diagnosed (non-autopsied) group of 26 cases, 21, or 80.8 per cent, had albuminuria and casts and five, or 19.2 per cent, albuminuria alone.

In the non-amyloid group, there were 35 patients with abnormal urinary findings and the most frequent specific renal disease among them was tuberculosis.

The commonest urinary signs in amyloidosis are albumin and casts. Their presence, even in the absence of other confirmatory data, strongly indicates amyloidosis provided tuberculosis of the kidney is excluded.

Congo Red Test: Bennhold (1923) [1] devised this test for the detection of amyloidosis. He believed that a positive test was one in which 60 per cent or more of the dye disappeared from the blood stream at the end of one hour. A negative test, he felt, does not rule out amyloidosis for small localized deposits especially in the kidneys alone may not be sufficient to give the typical result.

There is unanimity of opinion that 100 per cent elimination of the dye at the end of one hour is diagnostic of amyloidosis. However, this simply adds laboratory confirmation to what is already quite evident from a clinical standpoint in the majority of tuberculous cases, as indicating amyloidosis.

The Congo red test would be of more value if it enabled one to detect early cases of amyloidosis. Can it do so? In an attempt to answer this, we sought to determine first the rate of elimination of the dye from the blood

stream in normal individuals. Tests were performed in 25 cases. Regardless of body weight, each received 10 c.c. of a 1 per cent aqueous solution of congo red intravenously. Samples of blood were removed four minutes, one hour, two hours and four hours after injection. At the end of one hour, the minimum per cent of the dye removed from the blood was 14, the maximum 53 and the average 29.5. At the end of two hours, the comparable figures respectively were 17, 57 and 44.5. All but a trace of the congo red was eliminated at the end of four hours in all of the cases. A curve of the rate of disappearance of the dye, representing average values, is shown in figure 1. Thus, the average excretion of the dye in normals at the end of
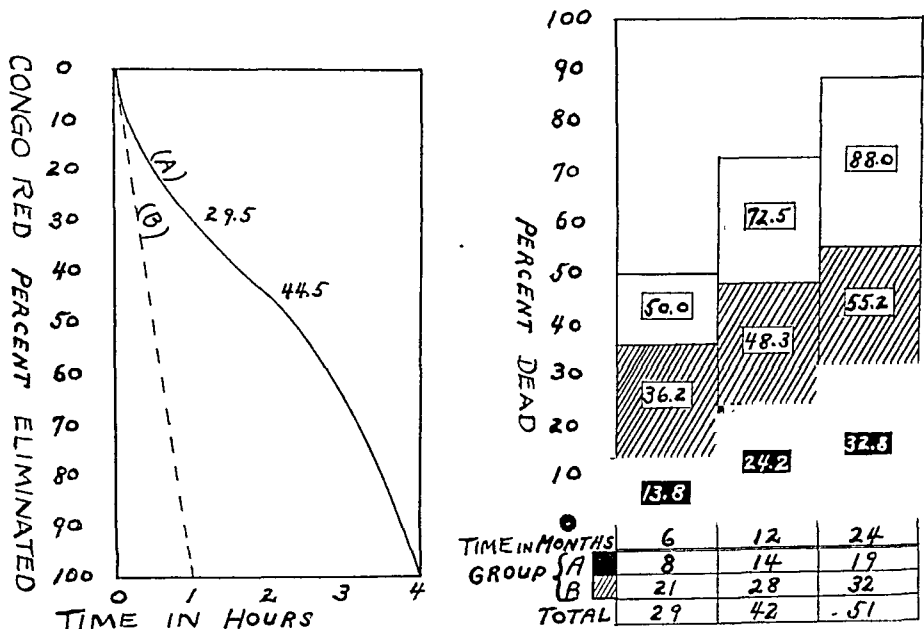
Fig. 1.

Fig. 2.

FIG. 1. Elimination of congo red from blood. A—Average curve in normals. B—Typical curve in amyloid cases.

FIG. 2. Duration of illness from abnormal urinary findings to death. Group A—clinically diagnosed cases. Group B—autopsied cases.

one hour is about one-third that of the definite case of amyloidosis. In fact, we have noted that some amyloid patients may absorb all of the dye in considerably less than one hour. We believe that 60 per cent removal from the blood is suggestive of amyloidosis but 100 per cent is diagnostic. We also believe that the test has definite limitations, because it is very difficult, according to our experience, to make accurate colorimetric observations in the intermediate zone between 60 per cent and 100 per cent. This impairs its usefulness for the diagnosis of early amyloidosis.

Next, we wish to refer briefly to some technical aspects of the test.

(1) How often can the test be repeated?

In a group of eight amyloid cases with 100 per cent dye retention, the congo red injection was repeated daily or every other day for several days

and in each case, 100 per cent absorption persisted. No toxic or cumulative effect was noted. We do not know what the saturation point is, if any, with congo red.

(2) One of the most important sources of error is the presence of hemolysis. To avoid this, we have resorted to the following:

(*a*) The use of an absolutely dry syringe and a large caliber needle.

(*b*) Heparin as the anticoagulant (Gerber and Fryczynski[2]).

(*c*) Prompt centrifugation of specimens. If, despite precautions, hemolysis occurs, the test is repeated in one or two days.

(3) In many cases, simultaneous determinations with the Bennhold and acetone technic (Friedman and Auerbach[3]) were made. The latter gave a consistently higher percentage of withdrawal of the dye from the blood; the acetone definitely "takes up" some of the dye. All but one of the congo red results mentioned in this paper were reported according to the Bennhold method.

Sixty-two of the 79 patients had congo red tests performed at intervals. These patients can be divided into two groups:

Group A: With 100 per cent retention of the dye in one hour—37 cases or 60 per cent. Thirty-two had albuminuria and casts, and in 12, or 35 per cent, these urinary findings antedated the first positive congo red test. This was so significant from the point of·view of early diagnosis that the same aspect was investigated in a group of 22 living amyloid cases. Proteinuria and casts preceded the first positive dye test in seven cases, or 31 per cent, and corroborated closely the above mentioned percentage.

Group B: Less than 100 per cent retention—25 cases (autopsied) or 40 per cent. Eighteen patients had albuminuria and casts. Thus it is seen that the examination of the urine could have furnished a better clue for the diagnosis of amyloidosis than the congo red test. Why did the test fail in this group? In 10 instances, it was done three months or more before death so that failure may have been due in part at least to the prolonged interval that elapsed. In 15 cases, the test was performed within a three month interval preceding death; three of these showed only minimal hepatic involvement and the remaining 12 cases had moderate to marked hepatic and multiple organ amyloidosis. The possibility of faulty technic in the performance of the test in this group should be considered.

III. PROGNOSIS

We believe that one of the best single objective findings in the early diagnosis of amyloidosis in a tuberculous subject is the presence, at first intermittently and later more persistently, of albumin and casts. Examination of the urine is a simple and universally used test, and although the above criteria are not a perfect guide, they are probably the least imperfect except

for 100 per cent congo red retention. However, the value of the latter is somewhat dissipated not only by the fact that it is a special test requiring careful technic but also because, from our material, albuminuria and casts antedated 100 per cent dye absorption in about one-third of the cases.

We, therefore, suggest that the onset of the abnormal urinary signs mentioned above may be used with a reasonable degree of assurance to indicate the approximate detectable onset of amyloidosis. With this yardstick, one
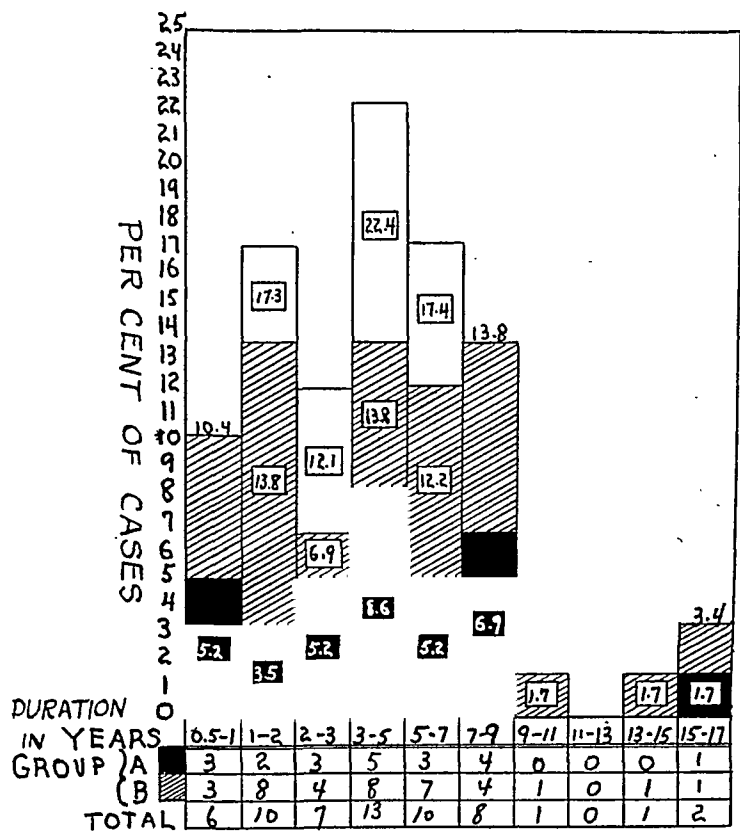
FIG. 3. Duration of illness from clinical onset of tuberculosis to abnormal urinary findings. Group A—clinically diagnosed cases. Group B—autopsied cases.

may then attempt to reconstruct the life cycle of these patients by dividing the duration of illness into two phases:

(1) from the clinical onset of tuberculosis to the onset of albuminuria and casts, and

(2) from the onset of these abnormal urinary findings (or amyloidosis) to death. The data in figures 2 and 3 are based on 58 cases of the entire group who had proteinuria and casts. The average total duration was 64.2 months. In the first period of illness, the average duration was 51.8 months, the minimum six months and the maximum 17 years. In the second phase, the average length of life was 12.4 months; 50 per cent of the patients died within the first six months, another 23 per cent in the next six months and an additional 15 per cent between the first and second years. In other words, 51

cases, or 88 per cent, were dead within two years after the development of amyloidosis. (This compares very closely with the 92 per cent mortality at the end of the same time interval reported by Pearlman.[4]) The estimated duration of amyloidosis in one of the remaining seven cases was as long as 10 years. This patient had arrested tuberculosis and died from uremia. It should be emphasized again that this recapitulation is only an approximate time table but nevertheless an enlightening one from a prognostic viewpoint. The prognosis in amyloidosis is greatly affected by the character and extent of the underlying tuberculous lesion.

IV. TREATMENT

Secondary amyloidosis has continued to be mainly a disease of diagnostic interest. Relatively little has been written about its treatment. As mentioned at the outset, the most important factor in the treatment is prevention. However, once amyloidosis develops, what therapy, if any, can be employed?

Before presenting our personal experiences, brief reference to some of the experimental and clinical reports pertaining to the treatment and reversibility of amyloidosis is warranted. Kuczynski[5] and later Morgenstern,[6] among others, noted resorption of amyloid in mice after injections of sodium caseinate were stopped, provided the lesion was not too far advanced. The latter author found some connective tissue replacement in the liver. Grayzel et al.[7] showed that a proper diet with an abundance of vitamins A and B would retard the production of amyloidosis in mice. Furthermore, the oral use of powdered whole liver produced resorption of moderate deposits of amyloid. Jaffé[8] noted that amyloidosis was prevented when cholesterol supplemented the stock diet. Letterer[9] found that amyloidosis developed more rapidly in animals whose water intake was restricted.

Gairdner[10] and Walker[11] each reported a case of regression of the clinical signs of amyloidosis. One followed amputation of a leg as the result of osteomyelitis, the other after obliteration of a chronic empyema by thoracoplasty. Reimann[12] reported the status of a patient with a controlled tuberculous lesion three years after thoracoplasty in whom clinical recovery was noted. Métraux[13] mentioned an interesting case of clinical recession which revealed slight anatomical healing in the liver only on autopsy examination. Habein[14] and Rosenblatt[15] also reported single cases of amyloid regression. Pearlman[16] similarly described four cases from a clinical point of view. Waldenström[17] reported punch biopsy studies of the amyloid liver with reversal in three cases after the healing of bone tuberculosis. Snapper and Ch'in[18] speculate on the influence of diet in amyloidosis. They mention its very low autopsy incidence (1.3 per cent) at the Peiping Union Medical College. The complete absence of dairy products and foods with high casein content from the diets of the population in Northern China may be an important factor in the infrequency of amyloidosis. Whitbeck[19] gave powdered whole liver (12 grams daily) over a period of two years to seven chil-

dren who were treated for bone and joint tuberculosis. After 18 months it was noted in five cases that the spleen and liver receded, albuminuria and edema disappeared, although the congo red test was still positive. This short review of the literature indicates:

(*a*) that experimentally induced amyloidosis of moderate degree may recede spontaneously after the causative irritant is removed;

(*b*) that there is clinical evidence in man of amyloid regression after control of the basic pathological condition is accomplished. Definite anatomical proof of regression is not yet convincing;

(*c*) that proper diet supplemented by a liberal intake of vitamins and liver may perhaps be of some value in the treatment of amyloidosis. This assumption stimulated the therapy phase of our study.

A. Material: The following report is concerned with 30 cases which had at least six months of treatment up to January 1942. Necessary treatment for tuberculosis was carried on pari passu. The group of 30 comprises 13 patients who are dead and included in the original series of 79 and in addition 17 living amyloid patients, eight of whom were still in the hospital and nine of whom were attending the out patient clinic.

B. Duration of Amyloidosis: The average span of life during the amyloid phase (computed to date of death, in living patients to January 1942) (table 3) was greater than the average duration noted in figure 2, but we

TABLE III

Duration of Amyloidosis

Treated Cases	Average	Minimum	Maximum
Dead (13)	20.2 mos.	6 mos.	6 yrs.
Living (Hosp.) (8)	20.1 mos.	7 mos.	3 yrs.
Living (O.P.D.) (9)	28.2 mos.	15 mos.	3 yrs.

cannot honestly state at this time that this increase was due to the therapy for amyloidosis alone.

C. Type of Underlying Tuberculosis: This must be considered in evaluating the results of treatment. The lesions have been classified as noted in table 4.

TABLE IV

Type of Pulmonary Lesion

Treated Cases	Slowly Progressive		Quiescent	Arrested	Empyema	Major Surgery	
	Mainly Unilateral	Mainly Bilateral				Thoracopl.	Extrapl. Pnx.
Dead (13)	2	11	0	0	3	3	1
Living (Hosp.) (8)	3	3	3	0	2	1	0
Living (O.P.D.) (9)	1	0	3	5	1	2	1

D. Treatment: 1. *Duration:* The period of treatment ranged from six to 36 months (table 5). 2. *Type:* Twenty-three patients received a combination of oral and parenteral therapy, whereas seven had medication by the former route alone (table 5). The basic oral therapy was as follows:

(*a*) high protein diet which is very important because of albuminuria;

(*b*) iron in the form of feosol, 9 to 12 grains daily for secondary anemia;

(*c*) dilute hydrochloric acid (90 minims daily). Gastric analyses were done in 28 patients of whom all but one showed either an achlorhydria or hypochlorhydria. No reappearance of free acid was noted in the former

TABLE V

Treatment

	Duration			Type		Results		
	Average	Minimum	Maximum	Parenteral	Oral Alone	Decreased Liver	Normal Urine	Normal Congo Test
Dead (13)..........	11.7 mos.	6 mos.	3 yrs.	11	2	0	0	0
Living (Hosp.) (8)...	16.7 mos.	6 mos.	32 mos.	4	4	0	0	0
Living (O.P.D.) (9)..	22 mos.	12 mos.	33 mos.	8	1	3	1	1

group. All had smooth tongues with varying degrees of papillary atrophy and three had associated glossitis. It has been shown that the gastric juice is normally an important element in the extraction of iron and vitamins from their natural food products (Sydenstricker [20]) Achlorhydria is common in all deficiency diseases and is believed to be a specific effect of nicotinic acid deficiency. In the three patients with glossitis, two received nicotinic acid (15 to 20 mg. daily for several days) and the third, amino acids intravenously which contain liberal amounts of nicotinic acid. All showed practically complete disappearance of the glossitis with marked improvement in the gross appearance of the tongue. These patients may have been suffering from a chronic deficiency (partial or complete) of the B vitamins which may be due not necessarily to an inadequate intake but rather to poor absorption and utilization of vitamins. The triad of anemia, lingual changes and depressed function of the gastric mucosa is commonly seen, of course, in non-amyloid tuberculous patients; but attempts at its correction were made on the assumption that amyloidosis which in itself is presumed to result from disordered metabolism might be benefited indirectly.

Supplemental parenteral therapy was given to 23 patients, 21 receiving liver extract, and two thiamin chloride. The former was used empirically, largely on the basis of the reports described above. The Lilly product was employed, each cubic centimeter containing 2 U.S.P. units which is equivalent to 25.5 grams of fresh powdered liver. The average dose was two cubic centimeters twice weekly (intramuscularly) during the hospital

stay and once weekly to out patient cases. It was difficult to determine a
definite maintenance dose. Since one may justifiably suspect impaired ab-
sorptive capacity of some of the nutritional requirements in these patients,
especially in the presence of intestinal tuberculosis, it was felt that parenteral
liver therapy might be expected to yield better results (if any at all were to
be obtained) than its oral administration. In five cases, thiamin chloride
(2 c.c.) was added to each dose of liver extract. Seven patients who refused
the injection therapy received vitamins and betaxin by mouth.

With the appearance of edema in 14 patients, treatment was augmented
by the restriction of fluid intake, salt poor diet and diuretics when necessary.
Considerable but usually temporary diuresis was obtained with ammonium
chloride and salyrgan or mercupurin. In a patient, however, with kidneys
damaged by amyloid, the repeated use of a mercurial compound would seem
like adding insult to injury. One patient with intestinal ulceration had a
bloody stool on three occasions after several courses of mercury.

3. *Results:* The following were the chief criteria employed in evaluating
the effects of therapy (table 5):

(a) significant reduction in size of liver or spleen;
(b) disappearance of albumin and casts;
(c) conversion from a positive to a negative congo red test confirmed
    by repeated injections.

In the dead and living hospitalized cases, there appeared to have been no
dramatic or essentially basic improvement in the amyloid status. Reduction
in edema, increased hemoglobin, elevated plasma protein level and better
appetite were beneficial signs temporarily noticed in some. Whether the
therapy may have tended to retard progression of the amyloidosis, we cannot
say. Four of the living out-patient cases, however, showed definite objective
improvement. Conversion to a normal congo red test was noted in one,
reduction in the size of the liver in three with disappearance of proteinuria
and casts in one of these. Moderate edema was present in one case for many
weeks but has not recurred in more than two years. Plasma protein and
cholesterol were maintained within normal limits. Liver extract was used in
two cases and thiamin chloride alone in the remaining two. The duration
of treatment in these cases ranged between 24 and 28 months.

How great a rôle the treatment actually played in producing these changes
is difficult to state. The dominant element may well have been the fact that
the underlying tuberculosis was in the process of being controlled when
therapy was started and later became arrested. It is possible that these
cases may have shown signs of clinical regression without any treatment
whatsoever.

Postmortem examination in five of the 13 patients who died showed no
definite evidence of anatomical regression of amyloidosis, including one
patient who received liver extract (6 c.c. weekly) for a period of three years,

Treatment of amyloidosis, as outlined above, in the presence of uncontrolled tuberculosis is uniformly disappointing. Adequate control of tuberculosis is a necessary prerequisite for better results. Treatment with proper diet, vitamins and liver extract may perhaps be of some value in combating amyloidosis in a select group of tuberculous patients in whom the basic disease is inactive or in whom there is at least a reasonable chance that it will become so in a relatively short time.

V. SUMMARY

A. Amyloidosis is a common complication of tuberculosis. The incidence in a group of 143 autopsied patients was 39 per cent.

B. A series of 79 cases of amyloidosis, which comprised 53 autopsied patients and 26 clinically diagnosed patients (nonautopsied) with 100 per cent congo red retention, is reviewed. Interesting clinical features are briefly presented. Significant laboratory findings and correlative studies are mentioned. A checkup of the urine examinations in 143 autopsied tuberculous cases was made; about 75 per cent of those who spilled albumin plus casts had amyloidosis. This is emphasized as a diagnostic criterion. Several aspects of the interpretation and technic of the congo red test are discussed. One hundred per cent absorption of the dye by the tissues, within one hour, is indicative of amyloidosis. A negative congo red test, however, does not exclude amyloid disease. Albuminuria and casts antedated 100 per cent congo red retention in about one-third of a group of 37 cases.

C. Charts are presented in an attempt to visualize the prognosis of 58 tuberculous patients, with amyloidosis, using the above urinary findings as connoting the probable "onset" of amyloidosis. According to this compilation, almost 90 per cent were dead within two years after the development of amyloidosis. The nature of the underlying tuberculous lesion greatly influences the span of life in the amyloid phase.

D. The status of 30 patients who received treatment for six months to three years for amyloidosis is reviewed. The basic oral therapy was a high protein diet, iron and dilute hydrochloric acid. Twenty-three also received parenteral therapy which was chiefly liver extract. Definite objective improvement in the amyloid status was found in four patients who had arrested tuberculous disease. Adequate control of tuberculosis was probably the chief factor in the improvement noted. There was no evidence of anatomical regression of amyloidosis in five autopsied cases.

BIBLIOGRAPHY

1. BENNHOLD, H.: Ueber die Ausscheidung intravenös einverleibten Kongorotes bei den verschiedensten Erkrankungen insbesondere bei Amyloidosis, Deutsch. Arch. f. klin. Med., 1923, cxliii, 32–46.

2. GERBER, I. E., and FRYCZYNSKI, M.: Use of heparinized blood in studies with congo red and bromsulphalein, Am. Jr. Clin. Path., 1942, xii, 312.

3. FRIEDMAN, M., and AUERBACH, O.: An improved congo red test for amyloidosis, Jr. Lab. and Clin. Med., 1935, xxi, 93.

4. PEARLMAN, A. W.: Amyloidosis; clinical and pathological study of 135 cases, Quart. Bull. Sea View Hosp., 1941, vi, 295.

5. KUCZYNSKI, M. H.: Edwin Goldmann's Untersuchungen über celluläre Vorgänge im Grund nachgelassener Präparate dargestellt und durch neue Versuche ergänzt, Virchow's Arch. f. path. Anat., 1922, ccxxxix, 185.

6. MORGENSTERN, Z.: Zur Frage über Amyloidose und Resorption, Virchow's Arch. f. path. Anat., 1926, cclix, 698.

7. GRAYZEL, H. G., ET AL.: Amyloidosis—experimental studies, Arch. Path., 1934, xvii, 50.

8. JAFFÉ, R. H.: Amyloidosis produced by injections of proteins, Arch. Path., 1926, i, 25.

9. LETTERER, E.: Studien über Art und Entstehung des Amyloids, Beitr. z. path. Anat. u. z. allg. Path., 1926, lxxv, 486.

10. GAIRDNER, W. T.: Discussion following Delafield's article on Diseases of the Kidneys, Trans. Assoc. Am. Phys., 1891, vi, 149.

11. WALKER, G. F.: A case of recovery from amyloid disease, Lancet, 1928, ii, 120.

12. REIMANN, H. A.: Recovery from amyloidosis, Jr. Am. Med. Assoc., 1935, cciv, 1070.

13. MÉTRAUX, P.: Über Rückbildungsvorgänge bei menschlicher Amyloidose, Frankf. Ztschr. f. Path., 1929, xxxvii, 279.

14. HABEIN, H. C.: Amyloidosis; report of a case in which the patient recovered, Proc. Staff Meet. Mayo Clin., 1934, ix, 261.

15. ROSENBLATT, M. B.: Recovery from generalized amyloidosis secondary to pulmonary tuberculosis. Report of a case, Arch. Int. Med., 1936, lvii, 562.

16. PEARLMAN, A. W.: Regression of amyloidosis, Quart. Bull. Sea View Hosp., 1940, vi, 92.

17. WALDENSTRÖM, H.: Quoted by MOSCHCOWITZ, E.: The clinical aspects of amyloidosis, ANN. INT. MED., 1936, x, 73.

18. SNAPPER, I., and CH'IN, K. Y.: Massive amyloidosis of both adrenal cortices; clinical syndrome with pathological findings, Chinese Med. Jr., 1940, lvii, 201.

19. WHITBECK, B. H.: Liver meal in the treatment of amyloidosis in surgical tuberculosis, Jr. Bone and Joint Surg., 1932, xiv, 85.

20. SYDENSTRICKER, V. P.: Clinical manifestations of nicotinic acid and riboflavin deficiency (pellagra), ANN. INT. MED., 1941, xiv, 1499.

CASE REPORTS

LIGATION OF A PATENT DUCTUS ARTERIOSUS WITH PROBABLE ENDARTERITIS; APPARENT CURE *

By J. W. Nixon, M.D., F.A.C.S., W. W. Bondurant, Jr., M.D., F.A.C.P., and Omer Roan, M.D., F.A.C.S., *San Antonio, Texas*

Unusual consideration is now being given in America to the surgical treatment of patent ductus arteriosus. One of us (Nixon) has recently reviewed the surgical aspects of the disease. Since the report of Touroff et al. of the cure of three cases of subacute *Streptococcus viridans* endarteritis following the successful surgical ligation of a patent ductus arteriosus, renewed interest has been shown in subacute endarteritis of this type. Their work definitely extends the benefit of surgical ligation of patent ductus arteriosus by offering a possible cure of this very serious complication. The report of an additional case successfully treated by operative means in which a sterile blood culture was obtained within a few minutes after the duct was ligated, therefore, seems warranted.

CASE REPORT

L. B., a white girl, aged nine, weight 56 pounds, was a full term child. Delivery was normal. There was no evidence of heart disease at birth. She had whooping cough at the age of three, but no other childhood diseases. At the age of six, upon entering school, a heart murmur was found by the school physician. Her tonsils were removed at that time. Her activity was not limited and her course in school was uneventful until December 1941, at which time she developed mumps. She returned to school after this attack and was in good health until January 16, 1942. At this time she developed a febrile illness with upper respiratory symptoms, thought to be influenza. Her temperature the first two days ranged as high as 104° F., and following this moderately severe infection she continued to have fever daily, the peaks ranging between 99° F. and 102° F. The same heart murmur which had been noted three years previously was still present. Until February 14, 1942, she was treated with various sulfonamide drugs without any evidence of improvement. On this date a roentgenogram was made which showed very slight prominence of the pulmonary conus (figure 1). A blood culture showed the presence of numerous colonies of *Streptococcus viridans*. On February 18, 1942, she was admitted to the Nix Hospital. When examined on this date the child showed considerable pallor. Blood pressure was 122 mm. Hg systolic and 72 mm. diastolic, pulse 116, temperature 100.2° F. Her heart was not enlarged. There was a loud continuous murmur heard best in the second left interspace about 6 cm. to the left of the midsternal line. The murmur waxed in intensity during systole and waned during diastole. It was typically machinery-like. The systolic component of this murmur was heard over the entire precordium, but was much softer. No thrill could be felt. The chest was clear. The spleen was definitely palpable, extending with deep inspiration two fingers' breadth below the left costal margin. There were three small areas on the hands and

fingers about 2 mm. in diameter which were bluish-red in color and apparently were the result of tiny emboli.

The urine varied in specific gravity from 1.009 to 1.022 and contained a trace of albumin, a few pus cells, an occasional hyaline and granular cast, and no red blood cells. The blood counts were as follows: February 18, 1942—Hemoglobin 72 per cent, red blood cells 4.56, white blood cells 6,980; differential: nonsegmented neutrophiles 6, segmented 61, lymphocytes 22, eosinophiles 6, monocytes 5. After several transfusions, on February 21, 1942 the blood count was as follows: Hemo-
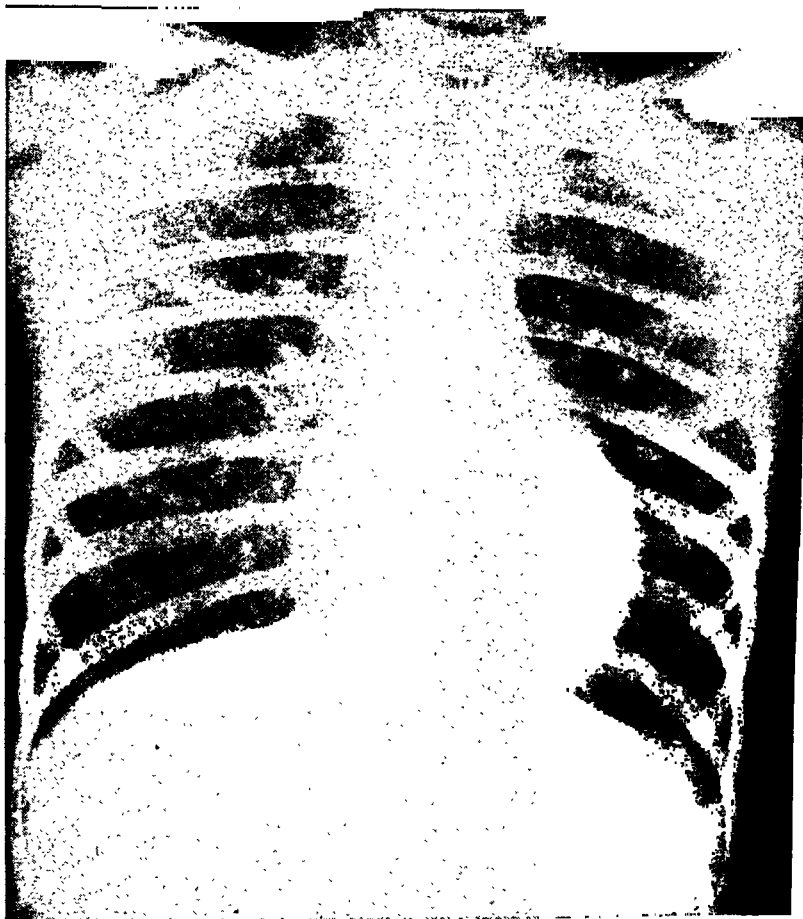
Fig. 1.   Roentgenogram of heart before operation.

globin 79 per cent, red blood cells 4.48, white blood cells 9,000; differential: nonsegmented neutrophiles 20, segmented 61, lymphocytes 13, monocytes 6. Blood cultures on February 18, 1942 and February 24, 1942 showed *Streptococcus viridans* in large numbers occurring in pairs and short chains. Her temperature showed an evening rise to 102° F., and in the morning varied between 99° and 99.8° F. Her pulse ranged between 110 and 140, respirations between 22 and 24. The diagnosis at this time was patent ductus arteriosus, *Streptococcus viridans* septicemia, *Streptococcus viridans* endarteritis. Sulfapyridine was administered in adequate doses for about 10 days with no effect on the temperature or pulse, then sulfadiazine was substituted. On March 17, 1942 the blood sulfadiazine concentration was 7.3 mg. per cent, the CO_2 combining power 49.3 volumes per cent. A blood culture at the same time showed a heavy growth of non-hemolytic streptococci and occasional colonies

of staphylococci. These latter were considered by the laboratory to be possibly a contaminant.

On March 24, 1942 an electrocardiogram was made (figure 2). The rate was 107, sinus rhythm, P–R 0.16, QRS 0.05. The electrical axis was plus 90.

Ligation of the patent ductus arteriosus had been urged since the middle of February. Inasmuch as she had shown no improvement, operation was finally agreed to and on April 13, 1942 she was admitted to the Santa Rosa Hospital. Her temperature was 100° F., pulse 140, respirations 26, and blood pressure 110 mm. Hg systolic and 70 mm. diastolic. The physical findings were the same as before. A blood culture on that day was positive for *Streptococcus viridans*.
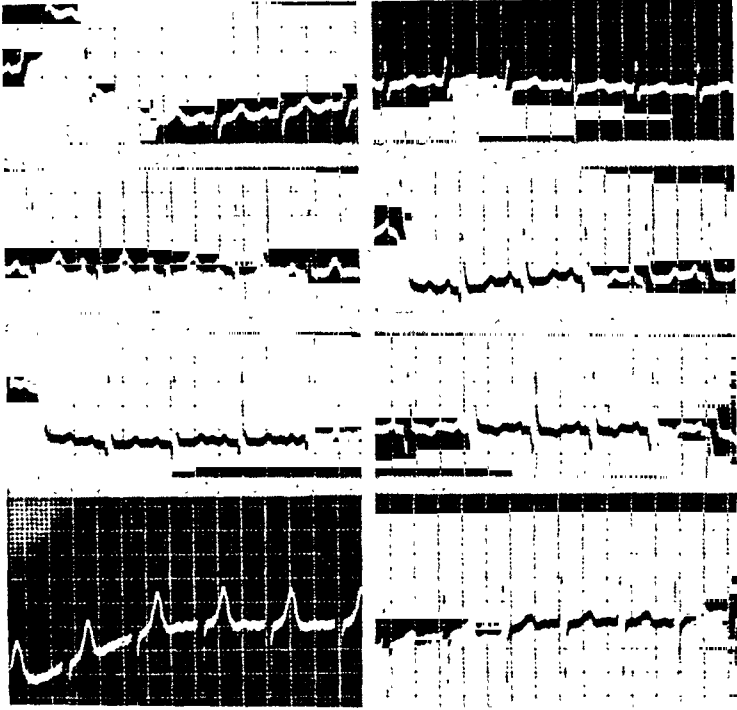
FIG. 2. Electrocardiogram before operation.

Operation: The patient was operated on April 14, 1942. She was placed on her back with a small pillow under the left shoulder, and with the left arm placed above her head. Cyclopropane anesthesia was administered by the intratracheal method. An incision was made on the left side of the chest, beginning at the lateral border of the sternum and extending laterally to the anterior axillary line over the right second costal interspace. The skin was incised, and the pectoralis muscles were cut in the line of the skin incision. The cartilages of the second and third ribs were cut just medial to the costo-cartilage junction. The pleural cavity was opened through the second interspace. The lung was collapsed and retracted posteriorly and downward, exposing the pericardium and mediastinum, along which could be seen coursing the phrenic nerve. The mediastinal pleura was picked up gently with fine forceps and was opened through an incision about two inches in length, beginning at the base of the lung and extending upward toward the neck. The fatty areolar tissue was carefully dissected away, exposing the pulmonary artery and the aortic arch. The thrill at its maximum was found to be over a vessel which extended from the pulmonary artery to the aortic arch, entering the aorta just opposite the left subclavian

artery. This structure was one and one-half centimeters in diameter and about two and one-half centimeters in length. It was carefully freed from the surrounding tissues by blunt dissection until the anterior, medial and lateral surfaces were freed and thoroughly exposed. A large aneurysm needle was carefully passed under this structure, separating it from the right bronchus. The lumen of this vessel was closed by traction on the silk which had been placed around it, and the condition of the patient was observed for a period of four or five minutes.

During the time that the vessel was held closed, the patient exhibited no untoward symptoms but the thrill disappeared as well as the murmur to which one of us (Bondurant) was listening through a sterile stethoscope. The diastolic blood pres-

Fig. 3. Roentgenogram of chest after operation.

sure, which had been 60 to 70 mm. Hg, rose to 90 mm. The pulse slowed somewhat. It was felt this was sufficient evidence to prove that the structure with which we were dealing was the ductus arteriosus, and it was accordingly doubly ligated with number eight braided silk. A small amount of oozing was encountered in the region of the recurrent laryngeal nerve, but this was controlled by pressure with moist gauze. No effort was made to close the mediastinal pleura because it was felt that if any oozing should occur it would be better to have it enter the thorax rather than to be held in the mediastinum. The lung was then inflated by positive pressure. The cartilage was sutured with No. 32 annealed wire. Two lengths of size No. 30 wire were passed around the second and third ribs, pulling them into apposition with each other. With continuous No. 1 chromic catgut locked sutures, the soft tissues were closed. The skin was closed with a continuous lock silk suture.

Postoperative Course: The patient was not shocked following the operation. She was placed in an oxygen tent only as a routine procedure in operations on chest cases. On the second postoperative day, 350 c.c. of blood-tinged fluid were removed from the left side of the chest. She was discharged from the hospital on the seventh postoperative day.

The patient was examined soon after the operation. There were no murmurs heard over the precordium nor over the pulmonary conus. On the second postoperative day the pulse was 120 and blood pressure 120 mm. Hg systolic and 102 mm. diastolic.

Four blood cultures were taken postoperatively and all were sterile. The first of these sterile cultures was taken 22 minutes after the duct was ligated. The second was taken three hours later, the third on the second postoperative day, and the last one on the day of her discharge from the hospital, April 20, 1942.

Temperature in the hospital ranged from 99.6° to 102.6° F. It was below 100° the last two days of her hospital stay, reached 100° her first day at home, and following that was continuously no more than 99°. Practically every afternoon and evening her temperature was 99°. Her pulse in the last few weeks was between 86 and 92. She has received none of the sulfonamides since the operation.

On May 20, 1942 the patient was again examined. Her blood pressure was 114 mm. Hg systolic and 80 mm. diastolic. Her appetite was good and she had gained some weight. She felt quite well. The heart was normal. The spleen could not be felt. A blood culture was attempted but because of previous punctures and venous thromboses the veins could not be entered. A roentgenogram of the chest (figure 3) showed an elevation of the left side of the diaphragm, probably from injury to the phrenic nerve by retraction. In the area of the pulmonary conus there was a concavity to the left. An electrocardiogram (figure 2) on this date showed an inversion of the T-wave in Lead III, and a Q-wave in Lead III. Some of the changes, both in the electrocardiogram and in the cardiac silhouette, were thought to be due to the considerable elevation of the left side of the diaphragm and consequent displacement of the heart.

SUMMARY

1. A case of patent ductus arteriosus with repeatedly positive blood cultures showing *Streptococcus viridans* is reported in some detail.

2. Sulfonamide therapy had no effect on the blood stream infection.

3. Ligation of the ductus arteriosus resulted in an almost immediate disappearance of the streptococci from the blood stream.

4. Although only five weeks had elapsed since the operation, and it was too early to make a definite statement, a cure seems to have been effected.

Addendum (November 12, 1943). Twenty months after the operation the patient has entirely recovered. She has had no elevation in her temperature above normal. No heart murmur is present, and she has gained twenty-eight pounds. She attends school where she takes part in light athletic games. One of us (Roan) removed a gangrenous appendix for her one year ago. Her recovery from that operation was uneventful.

MONOCYTIC LEUKEMIA ASSOCIATED WITH BONE CHANGES *

By ROBERT J. KOSITCHEK, M.D., *Los Angeles, California*

THE purpose of this paper is to present a case of monocytic leukemia which demonstrates the bone involvement previously observed in the lymphocytic and myelogenous types of leukemia. A review of the literature has failed to reveal similar bone involvement in leukemias in which the dominant cell is a monocyte or one of its immature forms.

Numerous accounts of bone changes in leukemia have appeared in the literature. In 1878, Newman and Eisenlohr [5] described pathological changes in the bones in leukemia. Subsequent reports of bone changes in myelogenous and lymphatic leukemia were made by Osler,[19] Snelling and Brown,[23] Doub and Hartman,[8] Poynton and Lightwood,[20] Karelitz,[14] Ewing,[12] Karshur,[15] Smith,[22] Ehrlich and Fover,[10] Baty and Vogt,[1] Clark,[2] Conybeare,[5] Connor,[1] and Craver and Copeland.[6]

In the case reports of monocytic leukemia by Reschad and Schilling-Torgau,[21] Dameshek,[7] Osgood,[18] Evensen and Schartum-Hansen,[11] Klumpp and Evans,[16] Jetter,[13] and in the reviews by Clough [3] and Osgood,[17, 18] no mention is made of bone changes.

CASE REPORT

R. P., male, aged 19, entered the Simpson Memorial Institute on September 28, 1938. The predominating symptoms were pain and limitation of motion in the right arm and shoulder, pain and weakness in both hips and thighs. The onset of the present illness was in May 1937, at which time the patient suffered from an upper respiratory infection. Physical examination at this time revealed a swelling in the upper left quadrant due to a very much enlarged spleen which practically filled the entire abdominal cavity. The white blood cell count was 307,200 per cubic millimeter.

The patient had one severe attack of epistaxis in May 1938. In September 1938, pain, dull aching and throbbing in type, appeared in both thighs and radiated anteriorly and posteriorly down to the knee. The patient experienced difficulty in walking, and was obliged to stiffen his knees when attempting to walk in a straight line. The pain became so severe that sleep was impossible without sedation.

The pain in the thighs was present on the day of admission, and the same type of pain was also present in the right shoulder with a resultant discomfort and limitation of motion. There had been a 10 pound weight loss in the previous three months.

During the 16 months that the patient was under observation before admission, his treatment consisted of ferric ammonium citrate, Fowler's solution, wheat germ oil, prontylin, Kinney's yeast extract, betalin, and Lilly's liver extract, and roentgen-ray therapy.

The patient had several courses of roentgen-ray therapy over the anterior, lateral, and posterior splenic ports, over the right and left axilla, right and left inguinal regions, and over both legs posteriorly. The dosage varied between 72 and 125 roentgen units and the time interval depended upon the patient's blood count and skin condition.

Physical examination revealed an emaciated, well developed adolescent male, subacutely ill, who appeared to be favoring a painful right shoulder. The patient walked with a shuffling, spastic gait, and the right shoulder was held in an "attention" attitude. The abdomen revealed an asymmetry with splenic and liver enlarge-

ment. The spleen measured 21 cm. in the anterior axillary line, extending below
the umbilicus on the left and 7.5 cm. to the right. The liver extended 6 cm. below
the right costal margin. The liver and spleen were firm, smooth, non-tender, and
freely movable. The upper extremities revealed limitation of motion of the right
arm, but complete range of motion with passive exercise. Pressure over the right
clavicle and shoulder elicited pain. The left arm was not abnormal. The lower ex-
tremities revealed pain and discomfort in the hips and thighs with movement. In
order to bend the knees the patient first extended his legs and then pushed with his
feet until proper leverage could be obtained. The patient was unable to move his
legs rapidly or coördinate the movements. The reflexes were physiologic in the
upper extremities; there was a loss of knee reflexes with normal plantar and Achilles

FIG. 1. Lesions present in the region of the surgical neck of the humerus. The lesions
are osteolytic in character and involve the medullary portion of the bone. Calcium with-
drawal from right clavicle with cystic formation.

reflexes in the lower extremities. A complete neurological examination of the upper
and lower extremities revealed no definite evidence of nervous system disease and no
evidence of peripheral neuritis.

Laboratory examination reports were as follows: The hemoglobin was 61 per cent
(9.5 grams, Sahli). The red blood cell count was 3,250,000 per cubic millimeter;
white blood cell count was 17,900 per cubic millimeter. The hematocrit was 28 per
cent. Examination of a film stained with brilliant cresyl blue and Wright's stain
revealed polymorphonuclear neutrophiles, adult, 33 per cent, young 16 per cent; meta-
myelocytes, 11 per cent; lymphocytes, 3 per cent; monocytes, adult, 3 per cent, young,
2 per cent; metamonoblasts, 21 per cent; non-classified blasts, 4 per cent; monocyto-
blasts, 2 per cent; eosinophiles, 3 per cent. The red blood cells appeared small. The
platelets were increased in number. There was a mild basophilia of the neutrophiles.*

* Blood findings were substantiated by Drs. Raphael Isaacs and S. Milton Goldhamer of
the Simpson Memorial Institute, Ann Arbor, Michigan.

Urine examination revealed no abnormalities. Bence-Jones protein was absent. The Kahn test for syphilis was negative. The stool examinations were negative for occult blood, ova, and parasites.

The roentgenographic report was as follows: Definite lesions were present in the region of the surgical neck of the humerus. These lesions were interpreted as osteolytic in character and involved the medullary portion of the bone. Less extensive changes were noted in the upper third of the femur proper—these changes might be due to osteoporosis. Osteoclastic changes were also noted in the right clavicle. In addition, it was noted that there was withdrawal of calcium in the medial portion of

FIG. 2. Circular areas of bone destruction in each ischium and about the right acetabulum. Suggestive changes in the iliac portion of the left acetabulum. A destructive process on the lateral margin of the lower right sacral segments. Similar changes in the head, neck, and inter-trochanteric region of each femur.

the right clavicle with some cyst-like formation which might well represent metastatic neoplasm in bone. Similar but less extensive osteoclastic lesions were seen in the surgical neck and head of the left humerus.

Stereoscopic studies of the pelvis showed circular areas of bone destruction in each ischium and about the right acetabulum. There were suggestive changes in the iliac portion of the left acetabulum. The sacrum was not well visualized because of overlying gas shadows; however, there was a destructive process on the lateral margin of the lower sacral segments to the right. Similar changes were seen in the head, neck, and inter-trochanteric region of each femur.

Routine examination of the skull showed several rounded areas of translucency representing bone destruction in the parietal region bilaterally. A similar area was seen in the inferior portion of the parietal bone anteriorly just above the squamous

portion of the temporal bone. Another area was seen just anterior to the fronto-parietal suture in its midportion on the right, and still another area was seen in the occiput on the left just inferior to the lambdoidal suture and near the midline. The internal auditory meatus on the right was larger than its fellow on the left, suggesting the possibility of neoplastic involvement. The sphenoid ridges and sella turcica were normal.

Examination of the spine showed a mild left dorsal scoliosis with no other evidence of abnormality. Antero-posterior projection of both forearms showed normal forearm, wrists, and metacarpals. The tibiae revealed no definite evidence of abnormality.

Course: During the first five days of hospitalization the patient's temperature varied between 100° F. and 103° F. Pressure, heat, and analgesics produced only temporary relief from pain in the right shoulder. On October 3, 1938 the patient was
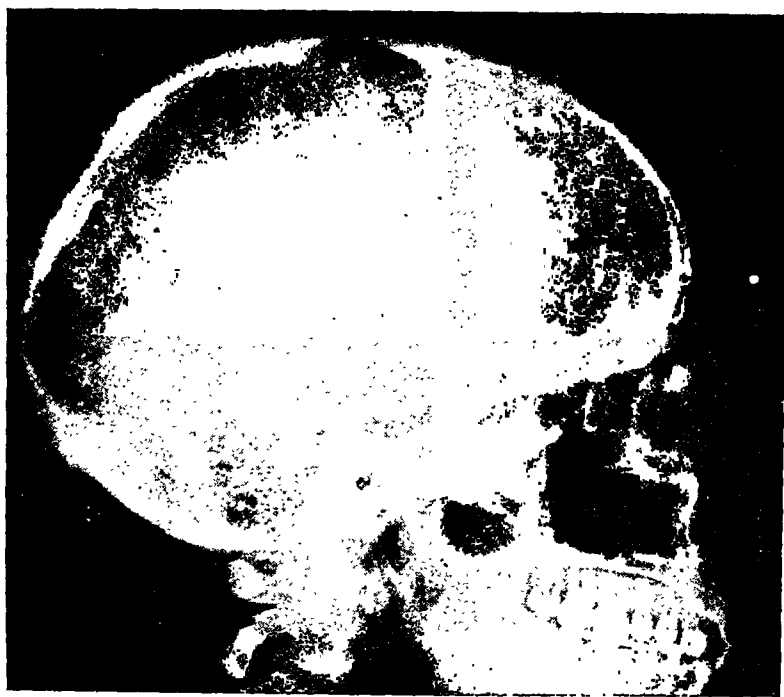
Fig. 3. Roentgenogram of skull, revealing several rounded areas of translucency representing bone destruction in the parietal region bilaterally. Similar areas seen in the inferior portion of the parietal bone anteriorly, anterior to the frontoparietal suture, and in the occiput just inferior to the lambdoidal suture.

given roentgen-ray therapy consisting of 400 roentgen units over an anterior right shoulder port. On the same evening the patient no longer felt pain or discomfort in the right shoulder and was able to sleep without sedation for the first time since admission to the hospital. On October 4, 1938, 400 roentgen units were given over the right shoulder posteriorly. That evening the patient voluntarily raised his right arm above his head and performed this action without pain. During the next four days the patient was given 400 roentgen units over each of four ports, two being anterior and two posterior. On October 9, 1938, the patient sat up in a chair for two hours. No further treatment was instituted, as it was felt that roentgen-ray therapy over splenic ports was contraindicated because of a white blood cell count of 26,100. On October 10, 1938 the patient became ambulatory, and was discharged on the morning of October 11, 1938. The hemoglobin maintained its level and on discharge was 59

per cent (9.1 grams per 100 c.c.) with a red blood cell count of 3,220,000 per cubic millimeter. At this time the patient experienced no pain or discomfort in the upper or lower extremities either on motion or at rest. The patient walked with a normal gait. He died January 1, 1939, at Michael Reese Hospital, Chicago, Illinois. No autopsy protocol was obtained.

DISCUSSION

There is still some doubt as to the existence of the so-called monocytic cell type of leukemia, but there appears to be sufficient evidence (Wainwright and Duff,[24] Doan and Wiseman,[9, 17, 18 and 8]) to establish the identity of this particular disease.

The case, as far as can be ascertained, is the first in the literature in which there was an associated monocytic leukemia and bone absorption. The softening and absorption in the medullary portion of many of the long bones, the increased porosity produced by the widening of the Haversean canals, and the cystic changes which may be indicative of neoplastic invasion have been noted in cases of lymphocytic and myelogenous leukemia, but are new to monocytic leukemia as a clinical entity.

The relief which was given to the patient by roentgen-ray therapy over the painful extremities leads to the suggestion that roentgenographic studies should be undertaken in cases of monocytic leukemia with painful bony areas.

CONCLUSIONS

1. A case of monocytic leukemia with neoplastic bone involvement similar to that observed in other types of leukemia is presented.

2. Roentgen-ray therapy when applied over the affected bony sites appears to be beneficial in relieving pain.

BIBLIOGRAPHY

1. BATY, J. M., and VOGT, E. C.: Bone changes of leukemia in children, Am. Jr. Roentgenol., 1935, xxxiv, 310.
2. CLARK, J. J.: Unusual bone changes in leukemia, Radiology, 1936, xxvi, 237.
3. CLOUGH, P. W.: Monocytic leukemia, Bull. Johns Hopkins Hosp., 1931, li, 148.
4. CONNOR, C. L.: Clinically demonstrable bone changes in leukemia, Am. Jr. Cancer, 1937, xxix, 20.
5. CONYBEARE, E. T.: Case of leukemia simulating acute rheumatism and Still's disease, Guy's Hosp. Rep., 1936, lxxxvi, 343.
6. CRAVER, L. F., and COPELAND, M. M.: Changes of bones in leukemias, Arch. Surg., 1935, xxx, 639.
7. DAMESHEK, WM.: Acute monocytic leukemia, Arch. Int. Med., 1937, xlvi, 718.
8. DOUB, H. P., and HARTMAN, F. W.: Lymphocytic, myelocytic and monocytic neoplasms; roentgen diagnosis and treatment, Jr. Am. Med. Assoc., 1935, cv, 942.
9. DOAN, CHARLES A., and WISEMAN, B. K.: The monocyte, monocytosis, and monocytic leukosis, ANN. INT. MED., 1934, viii, 383.
10. EHRLICH, J. C., and FOVER, S.: Periosteal ossification in myelogenous leukemia, Arch. Int. Med., 1934, liii, 938.
11. EVENSEN, O. K., and SCHARTUM-HANSEN, HALL: Monocytic leukemia, Acta med. Scandinav., 1938, xcvi, 129.
12. EWING, J.: Neoplastic disease, 1922, W. B. Saunders Co., Philadelphia.

13. JETTER, WALTER W.: Acute monocytic leukemia, Med. Rec., 1937, ccxlvi, 429.

14. KARELITZ, S.: Unusual form of periosteal elevation, Am. Jr. Dis. Child., 1927, xxxiii, 394–403.

15. KARSHUR, R. G.: Leukemia blood picture with roentgen changes in bone, California and West. Med., 1931, xxxv, 125.

16. KLUMPP, THEODORE G., and EVANS, THEODORE: Monocytic leukemia, Arch. Int. Med., 1936, lviii, 1048.

17. OSGOOD, C. W., and LYGHT, C. E.: Monocytic leukemia, Jr. Lab. and Clin. Med., 1933, xviii, 612.

18. OSGOOD, E. E.: Monocytic leukemia, Arch. Int. Med., 1937, lix, 931.

19. OSLER, WM.: The principles and practice of medicine, 1892, D. Appleton, New York, p. 696.

20. POYNTON, F. J., and LIGHTWOOD, R.: Lymphatic leukemia with infiltration of bone marrow simulating acute rheumatism, Lancet, 1932, i, 92.

21. RESCHAD, H:, and SCHILLING-TORGAU, V.: Ueber eine neue Leukämie durch echte Uebergangsformen und ihre Bedentungvfür die Selbständigkeit dieser Zellen, München. med. Wchnschr., 1913, lx, 1981.

22. SMITH, C. H.: Leukopenic myeloid leukemia associated with arthritis, Am. Jr. Dis. Child., 1933, xlv, 123.

23. SNELLING, C. E., and BROWN, A.: Bone changes in leukemia, Arch. Dis. Child., 1934, ix, 315.

24. WAINWRIGHT, CHARLES W., and DUFF, G. LYMAN: Monocytic leukemia, Bull. Johns Hopkins Hosp., 1936, lviii, 267.

HYPERTENSION CAUSED BY UNILATERAL KIDNEY DISEASE *

By J. SHIRLEY SWEENEY, M.D., Sc.D., F.A.C.P., and JOHN M. PACE, M.D.,
Dallas, Texas

NUMEROUS reports of unilateral renal disease associated with hypertension have appeared in the literature since the epochal researches of Goldblatt. The purpose of this report is to add to the literature one more case of what seems to be a perfectly typical atrophic kidney which was associated with marked hypertension.

CASE REPORT

The patient, Miss M. J. M., aged 21, consulted one of us on May 3, 1941. She was referred by her family physician because of high blood pressure. Her family history was entirely negative. Her menstrual history likewise was perfectly normal. Her only illness during childhood was measles, except for some kidney trouble, the nature of which was not clear. She stated that she was in bed for several days but that there was no edema nor was there blood in the urine. She had had an occasional attack of tonsillitis. Her tonsils and adenoids had been removed in 1940. She also had had an operation for acute appendicitis at the age of 13.

Her complaint when first seen was that of headache. She stated that she had not felt well for the past six or seven months, having experienced fatigue and general malaise.

Her headaches were basal in location and were present each morning on awaking. During the latter part of 1940 she developed an upper respiratory infection and at this time the physician who attended her took her blood pressure and found it to be 230 mm. Hg systolic and 120 mm. diastolic. From that time until I first saw her she

FIG. 1. Low power view of kidney cortex showing patchy condensation of parenchyma due to loss of glomeruli and tubules, and resulting scarring. Numerous small mononuclear inflammatory cells are seen in these frequent scar areas. The glomeruli and tubules in the intervening uninvolved areas show no significant changes.

had lost about 12 pounds, was quite nervous, and complained of considerable fatigue in addition to her headaches.

Physical examination revealed a rather thin, undernourished individual. There was considerable discoloration in the form of vasomotor reactions in her hands.
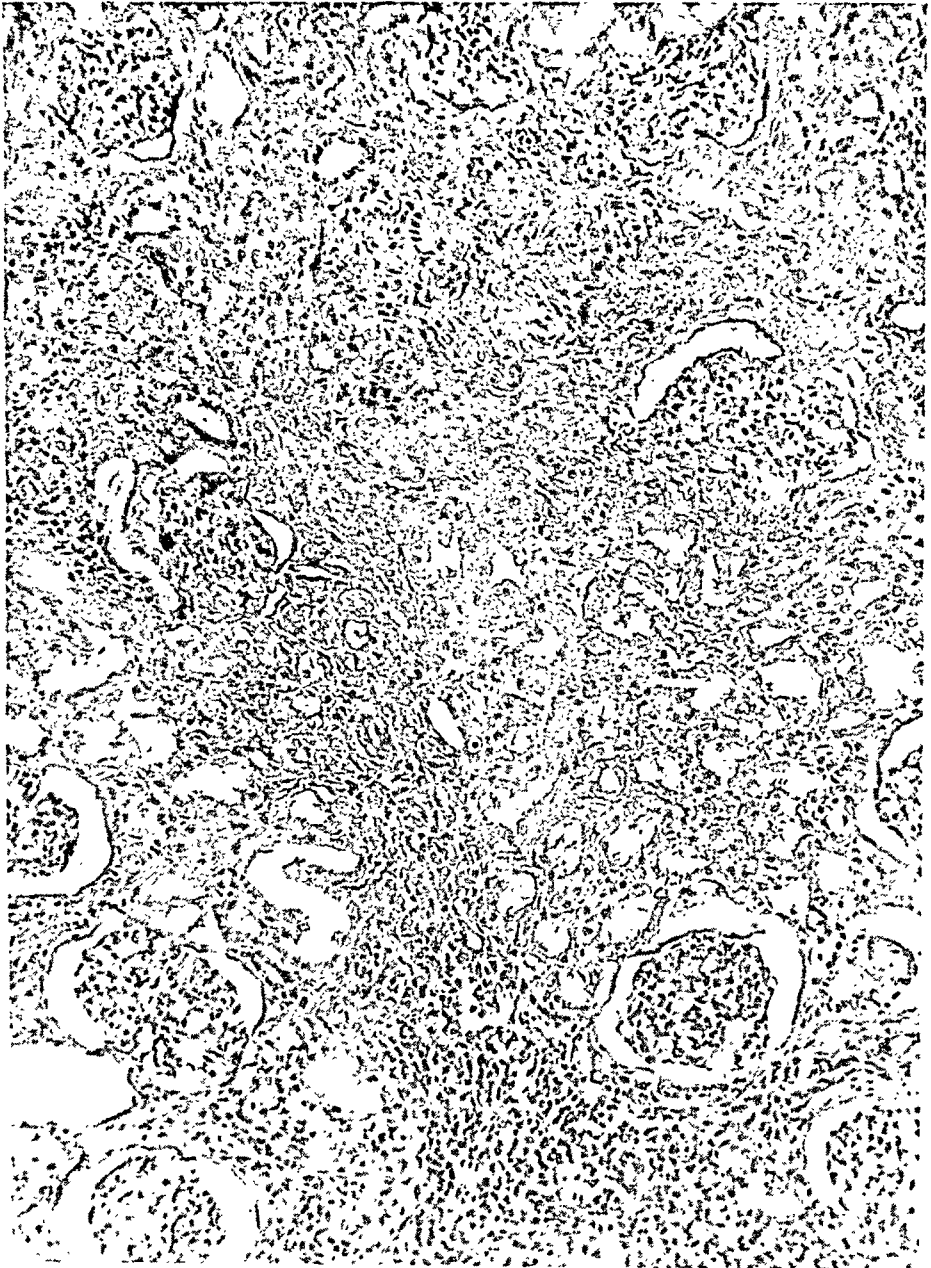
FIG. 2. In addition to the changes noted in figure 1, this low power view of kidney parenchyma shows thickening of the blood vessel walls with marked narrowing of the lumina.

There were some brownish pigmentations about her face, neck and forearms. Ophthalmoscopic examination revealed considerable tortuosity of the retinal vessels and there were areas where definite arterial spasm was noted. The vessels were moderately narrowed and there was some loss of light reflex. The discs were sharply

outlined. Ocular movements and fields of vision were normal. The pharynx was slightly congested. The teeth appeared more or less chalky. The submaxillary glands were palpable, as was the isthmus of the thyroid gland. There was some tenderness on fist percussion of the right kidney. Heart sounds were regular, distinct and quite forceful, with accentuation of the aortic second sound. The pulse rate was 100. The abdomen was scaphoid and negative except for a short McBurney scar. The left colon was palpable. There was no edema. Vibratory sense was normal. The hands were cold, discolored and moist. There was no tremor present. The pelvis was negative, as was the rectal examination. Blood pressure was 224 mm. Hg systolic and 154 mm. diastolic.

Lateral stereoroentgenogram of the skull revealed a normal sella turcica. There was a marked trace of albumin in the urine, a few hyalin casts, and an occasional red cell. Blood count was entirely normal. Blood urea nitrogen was 16 mg. per cent. Urea clearance was 127 per cent of normal. Phenolsulfonphthalein excretion was 82.4 per cent. Perirenal air studies were done and revealed nothing of consequence. A roentgen-ray film of the abdomen revealed a relatively small kidney on the right.

Dr. John M. Pace then investigated more thoroughly her urinary mechanism. Catheterized bladder urine was found to contain a small amount of albumin and granular casts. Cystoscopic examination was performed and indigo carmine was returned from the left ureteral orifice in a grade three concentration in 10 minutes whereas only a faint trace of blue was noted from the right ureteral orifice.

A retrograde pyelogram of the right side revealed a small kidney outline approximately one-half the size of the opposite kidney with a normal pelvis and calices. The left retrograde pyelogram was considered quite normal. Cystoscopy was repeated on the following day with the same findings as to the return of the indigo carmine. About 10 days later excretory urograms were made using Neo Iopax and good visualization was obtained of each kidney in five, 15 and 25 minute films.

About two weeks later the patient was subjected to another cystoscopy. Phenolsulfonphthalein was used intravenously and at the end of 45 minutes time 22 per cent of the dye was returned from the left kidney and none from the right.

This patient was observed for approximately two months, particular attention being paid to eye grounds and blood pressure. Her systolic pressure ranged from 210 to 240 mm. Hg and the diastolic level varied from 120 to 140 mm. Hg.

About the middle of June a definite fuzziness of the discs was noted. The patient at this time complained also of mild visual disturbance. She was advised that insofar as the right kidney was functionless, she had much to gain and nothing to lose by having it removed. She decided upon operation and on July 8 a nephrectomy was performed.

The removed kidney was approximately one-third its normal size. When the patient was returned to her room following operation, her blood pressure was 145 mm. Hg systolic and 85 mm. diastolic. Four hours later it was found to be 132 mm. Hg systolic and 100 mm. diastolic. The following morning her tension was 130 mm. systolic and 78 mm. diastolic. Twelve days later when she was discharged the reading was 126 mm. systolic and 78 mm. diastolic.

The kidney grossly was considerably smaller than normal. It measured 10 by 4 by 3 cm. and weighed 60.6 grams. The capsule was thickened but stripped readily and underneath there was a smooth shiny surface. On section the cortex and medulla were very well defined. The cortex averaged 4 mm. in thickness. There was no gross scarring in the parenchyma. The kidney pelvis was not enlarged. There were no stones.

Microscopically, sections through different portions of the kidney revealed very extensive focal chronic inflammatory changes immediately beneath the capsule (photo-

micrographs 1 and 2). In these areas was seen marked condensation of renal tissue with patchy scarring and with loss of tubules and glomeruli. A heavy small mononuclear cell infiltration occurred in these areas. Glomeruli in different states of degeneration were noted, whereas in striking contrast in the remainder of the renal parenchyma the glomeruli were essentially normal. The sectioned blood vessels were noticeably thickened, their lumina being reduced as much as one-third in diameter in numerous areas (photomicrograph 2). A section through the pelvis of the kidney revealed slight overgrowth of the pelvic mucosa. A few scattered chronic inflammatory cells were noted beneath. The pathologist, Dr. John L. Goforth, rendered the opinion that there was a chronic active progressive subcapsular pyelonephritis of marked degree.

The patient was seen on numerous occasions following her operation. Approximately two months following operation her eye grounds were strikingly different from the preoperative condition. The fuzziness had entirely disappeared about her discs, there was definite return of some light reflex and the spasm previously noted was absent.

Her blood pressure varied from 110 to 116 mm. Hg systolic with a diastolic of 72 to 78 mm. The patient gained 15 pounds and went back to her work. She was carefully checked in February 1942 at which time her blood urea nitrogen was 10 mg. per 100 c.c. and her urea clearance was 124 per cent of normal. Repeated urine examinations revealed nothing of consequence. Phenolsulfonphthalein excretion was 50 per cent in the first hour and 9 per cent in the second.

This patient presented only one interesting symptom following her operation, which was that of a momentary dizziness on arising from a recumbent position. This dizziness was rather marked a few months following operation but gradually became less severe, and when last seen the patient was entirely free of this annoyance. The only explanation one might offer for this interesting symptom is the obvious lack of cardiac and vascular adaptation to the changed levels of blood pressure. It is believed that this patient will continue a well individual; and she will be frequently observed for any possible disease in the remaining kidney.

SUMMARY

A case of hypertension has been reported in detail which was apparently a result of unilateral kidney disease. The pathologic lesions of the kidney were comparable to those of the Goldblatt and Page experimental kidneys in hypertensive dogs.

For approximately one year the patient has been perfectly normal as far as blood pressure and general health are concerned.

Addendum: Since this case report was submitted, the patient has married and has given birth to a 7½ lb. baby with no difficulty. All during her pregnancy her blood pressure was watched carefully and the maximum reading was 122/82. Most of the readings varied from 106 to 110 systolic. Her kidney function remained quite normal throughout the period of gestation.

CHRONIC HYPERTROPHY OF THE SKIN AND LONG BONES: AN OSTEO–DERMOPATHIC SYNDROME *

By IRVING LEINWAND, M.D., and A. WILBUR DURYEE, M.D., F.A.C.P.,
New York, N. Y.

In 1926 M. Labbé and P. Renault [1] observed a case of "hypertrophic osteo-dermopathology." In 1927 Gronberg [2] described the syndrome "Magalia cutis et osseum." He collected nine similar cases from the literature in the preceding 16 years. In 1935, Touraine, Solente and Golé [3] designated and described "un syndrome osteo-dermapathique." This syndrome is characterized by lesions of thickened skin with furrowing of the scalp, forehead, face, and extremities associated with elephantiasis of the long bones without involvement of the joints. They reported several cases which had been previously classified as dermatological, associated with a pulmonary osteoarthropathy. These skin lesions were usually diagnosed as cutis verticis gyrata or pachyderma vorticella. Since these original reports Meilberger,[4] Roy,[5] Rintelen,[6] and Giomo [7] have reported cases of pachyderma with periostosis of the extremities, most of which, however, were associated with an elephantiasis of the eyelids.

Touraine et al. state that there are three clinical forms of their syndrome: the complete, the incomplete, and the incipient. In all these forms the skin lesion is pronounced (although there may be no scalp lesions in the incomplete form) and the bone lesions vary from extensive to slight changes and even complete absence. The characteristics of this syndrome are:

1. It affects young adults beginning before the twentieth year and is most apparent between 20 and 30.
2. It is limited to males.
3. It is not related to occupation. There is no familial history or history of syphilis.
4. The general health is not affected.
5. The skin becomes thick and furrowed especially over the forehead, face, scalp, hands and feet. No other parts of the body are affected.
6. There is a thickened periosteum which is bilateral and symmetrical.
7. The extremities show considerable hypertrophy due to thickening of the skin and periosteum.
8. The hands are enormous.
9. The nails are rounded like watch crystals.
10. There is normal mental state and no loss of libido.

Histological study of the involved tissue uniformly shows:

1. Enlarged excretory canals of the sebaceous glands.
2. An increase in the size and number of the sweat glands with tortuosity and lengthening of the excretory canals.

3. An increase in the size and number of elastic fibers in the corium.
4. The blood and lymph vessels may be normal but are more often enlarged.
5. There are frequently inflammatory infiltrations about the hair follicles, sebaceous glands, and blood vessels. These may sometimes form small areas of necrosis.
6. The subcutaneous fatty tissue is usually normal.

CASE REPORT

A white male, aged 46, born in Italy, was admitted complaining of progressive difficulty in walking, and swelling of feet and legs, hands and forearms of nine years' duration.

FIG. 1. (*Left*) Patient A.D. Hypertrophy of extremities due to thickening of skin and periosteum. Note sharp demarcation of joints.

FIG. 2. (*Right*) Patient A. D. Mild hypertrophy of hands and forearm without clubbing of fingers. Note accentuation of thenar folds.

Onset and Course: The present condition began about nine years prior to admission with pain in the left ankle. Then in chronological order the right wrist, left wrist, and the other ankle were involved. This was followed in a short time by swelling of the legs and then the forearms. There was no history referable to the vascular system such as claudication or rest pain except for an occasional twinge of pain in the knees. There was no history of phlebitis or varicose veins.

Past History: There had been no serious illnesses except for a fracture of the tibia and fibula of the left leg in 1922.

Family History: There was no history of any similar condition in any member of his family, past or present. There was no family history of vascular diseases, diabetes, syphilis, or tuberculosis.

Personal History: His occupation was that of a general building worker. He had been unemployed for several years. His habits were normal. He smoked cigars occasionally.

FIG. 3. Patient A. D. Thickening of skin over face with increased fold over forehead.

Review of Systems: All were negative except as noted in the chief complaint.

Physical Examination: This revealed a well developed, well nourished male about 45 years of age with thick coarse skin of light copper color. Mental reactions were slightly slowed. The nose, ears, and head were normal in size and proportion. There was no enlargement nor protrusion of the jaw.

Eyes: The pupils were equal and regular, reacting to light and accommodation. No abnormalities were noted in the fundi.

Nose and Ears: There was no obstruction nor discharge.

Chest: The chest was symmetrical and expansion was equal.

Heart: There were no murmurs. There was regular sinus rhythm. The point of maximum impulse was in the fifth interspace in the midclavicular line.

Lungs: Breath sounds and resonance were normal.

Abdomen: There was no rigidity, tenderness nor palpable mass. The liver, kidney and spleen were not palpable.

Scrotum: There was an edema of moderate degree.

Rectal: The prostate was small; the median sulcus was palpable. The epididymis on the left side was hard and indurated, but not tender.

Extremities: There was a marked brawny edema of the legs extending from the knees down to and including the feet, and of the forearms from the elbows down to and including the hands (figures 1 and 2). There was some pitting on deep pressure. The joints were only slightly involved in this swelling so that the lines marking the margins of the joints were greatly accentuated because of the surrounding edema. The skin was noticeably thickened in the extremities as well as over the face (figure 3). There were several small bluish discolorations on the legs. There was no clubbing of the fingertips nor of the toes.

This patient had been treated at another hospital in 1931 and again in 1937. The following diagnoses were received from this institution. *1931 Diagnosis:* Old fracture of the left tibia and fibula. Roentgenogram showed no evidence of fracture of bones of the foot. *1937 Diagnosis:* Retained roots; diseased tonsils; old healed fracture of the left tibia and fibula; infected ingrown toe nail; no evidence of thyroid disease. Laboratory: Basal metabolic rate plus 10; blood Wassermann reaction negative; blood chemistry normal; electrocardiogram showed left axis deviation.

Further laboratory studies were: Sedimentation rate (Westergren method) 54 mm. in one hour. Inorganic phosphate 2.3 mg. per cent (normal 3.5–4.0). Calcium 10.1 mg. per cent (normal 9.6–11.0). Phosphatase activity 4.8 units 2 hr. incubation (normal 3–5). Total serum protein 4.9 per cent; albumin 3.5 per cent; globulin 1.4 per cent; ratio 2.5.

Blood Wassermann negative on June 29, July 26 and August 17, 1939; Kline diagnostic test (July 24, 1939), negative. Kline exclusion test (July 24, 1939), plus-minus. Blood chlorides 480 mg. per cent (NaCl); blood cholesterol 185 mg. per cent; red blood cells 3,830,000, hemoglobin 12.35 gm. (74 per cent); white blood cells 8,800, color index 0.97. Differential: Polynuclear neutrophiles 65, polynuclear eosinophiles 3, monocytes 11, lymphocytes 21.

Repeated urinalyses were negative except for occasional white blood cells. Culture of the prostatic secretion on November 29, 1939, was positive for *Staphylococcus albus.* On November 22, 1939, test for hormones in the urine was strongly positive for Prolan.

Further blood chemistry determinations were:

	N.P.N.	Ca.	P.	Glucose	Protein	Phosphatase	Cholesterol
	in mg. per cent				per cent	units	mg. per cent
January 8, 1940......	36.6	9.6	3.8	88.0	7.29	3.58	
February 4, 1940......		10.0	2.4		Alb. 4.32 Glob. 2.97		
February 5, 1940......		10.0				2.36	159.0 Esters 86.5

Physical Measurements:

	Legs and Arms			
	Right		Left	
	August 3, 1939	March 25, 1941	August 3, 1939	March 25, 1941
Above malleolus..............	11.0	10.5	11.75	12.0
4½ in. below patella...........	14.85	15.6	16.12	16.25
Lower margin patella..........	15.12	14.6	14.36	14.5
Upper margin patella..........	16.5	17.5	16.12	17.0
Above wrist..................	8.0	8.5	8.36	7.75
1 in. below antecubital fold.....	11.5	12.0	11.25	11.75
1 in. above antecubital fold.....	11.0	11.5	10.25	11.25

Weight on admission was 175 lbs., June 29, 1939. Weight at present, February 24, 1941, is 190.

Oscillometric readings:

	Right	Left
Foot.......................	⅝	¾
Ankle....................	2.0	1¾

Course: This patient was followed in the Out Patient Department for a period of six months. During this period he was on a salt free diet. An attempt was made to reduce the edema by acetyl beta methyl choline chloride (mecholyl) therapy given by iontophoresis, and by physiotherapy. This was entirely ineffective. At the end of this period he was hospitalized for more complete study.

Because of the finding of urinary Prolan, androgenic therapy in the form of testosterone propionate was instituted and he was given 25 milligrams three times weekly. He received a total of 2025 milligrams over a period of 27 weeks. This was supplemented by the empirical use of nicotinic acid, thiamine chloride, and other factors of the B complex orally. Physiotherapy in the form of whirlpool baths and massage was also given.

In November 1940, almost one year after admission, the patient suddenly developed a temperature of 104° F., with a marked irregular reddening of the right arm. This completely subsided in 10 days with sulfanilamide therapy. Except for this incident, the patient's condition remained practically the same during the 21 months of observation. There was some softening of the brawny edema but no marked decrease in the size of the extremities. Roentgenographic studies at various intervals revealed no significant deviation from the original picture in the 13 months following admission. There was revealed some decrease in the amount of periostitis with moderate smoothening of the irregular margins. There was some recent rarefaction of bones of the hands and feet with formation of a cyst in the cuneiform bone. The skin did not appear to be as coarse or as thick. Altogether the changes were not remarkable. During the period of observation, laboratory tests remained consistently normal except for an elevated sedimentation rate.

Biopsy of Skin, Periosteum and Bone, December 11, 1939 (figures 4 and 5). *Microscopic:* Skin sections were covered with stratified squamous epithelium. The corium was much increased by thick fibers of hyaline fibrous tissue as in old scars. The elastic fibers were fragmented and appeared thinned near the surface, and thickened and knotted in the deeper layers. The sweat and especially the sebaceous glands were hypertrophied with parakeratosis in the ducts.
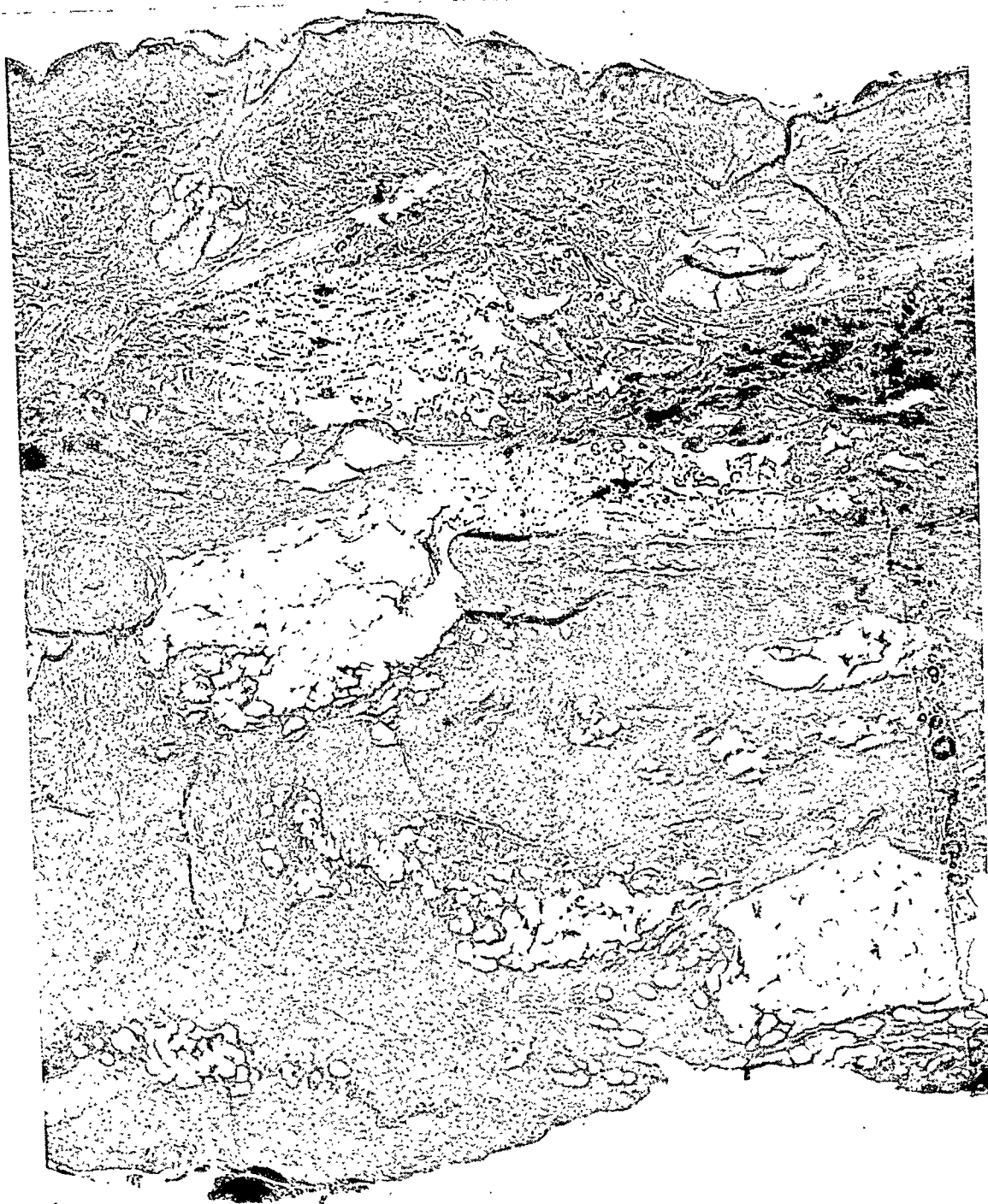
FIG. 4. Biopsy of skin from pretibial area of the right leg.

The bands of fibrous tissue union with the subcutaneous fascia were thickened. Here, the blood vessels had edematous walls with swelling and exfoliation of the intimal endothelium. At one point in the subcutaneous fascia there were several areas of calcific stippling.

FIG. 5. Biopsy of right tibia.

The union of muscle bundles and fascia and periosteum was marked by prolifera-
tion of mesothelium and capillaries. Some vessels were surrounded by dense foci of
lymphocytes and plasma cells and polynuclear leukocytes were occasionally seen in
the vessel lumens. Lesser but similar changes were seen in the fascial strands ex-
tending through the fat from fascial layer to layer, and rarely between the muscle

fibers. The parperiosteal tissue showed the most elaborate foci formed chiefly of plasma cells, some of which were seen about the smallest capillaries. In these foci some cells were filled with old blood pigment.
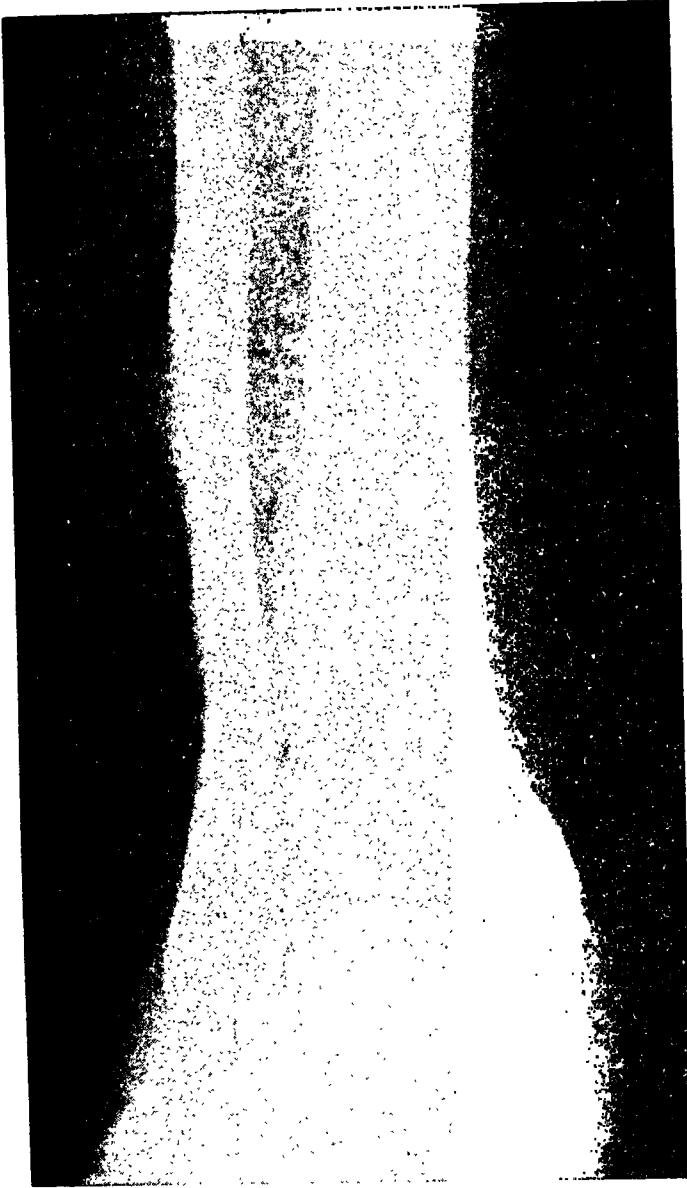
FIG. 6. Roentgenological study of right lower extremity. Note marked periosteal irregularity of both tibia and fibula.

The sections of decalcified bone showed a porositic cortex with the marrow spaces enlarged. The periosteal surface suggested some slight previous activity, i.e., young periosteal cells but no osteoclasts, now quiescent.

Diagnosis: Chronic productive dermatitis with hyperplasia of glands. Chronic productive inflammation of parperiosteal tissues, parosteitis. Osteoporosis.

Differential Diagnosis: Due to the predominance of the periosteal lesion and bone changes in this case several other conditions must be considered.

Hypertrophic Pulmonary Osteo-arthropathy. This was first described as an "ossifying periostitis" in 1889 by Bamberger.[8] This was closely followed in 1890 by Pierre Marie,[9] who described a series of cases called "osteoarthrompthie hypertrophiante pneumique." Since that time some 150 cases have been reported in the literature, less than 10 per cent of which were without a primary disease such as pulmonary tuberculosis, congenital heart disease, etc.[10] In this disease one usually finds: (1) The presence or history of some respiratory or heart disease. (2) Usually no enlargement of the soft parts of the extremities except for clubbing or bulbous swelling of the tips of the fingers and toes. (3) Symmetrical deposits of new subperiosteal bone. (4) Sometimes sclerosis and thickening of the cortex. (5) Curving of the nails in all directions. (6) Atrophy of the cancellous tufts and elongation of the terminal phalanges, often with hairlike calcareous strands projecting toward the nail.

Familial Acromegalic-Like Skeletal Disease. Previous to and following the work of Bamberger and Marie, Arnold,[11] and later Oehme [12] and Muller,[13] and more recently Freund [14] described a condition which they called idiopathic familial generalized osteo-phytosis or familial acromegalic-like skeletal disease.

The differential characteristics are: (1) Onset of the disease at puberty. (2) Progression by exacerbation. (3) Extreme degree of bony change. (4) Tendency of the syndrome to be familial. (5) Very little if any thickening of the soft tissues. (6) Clubbing of the finger tips.

Acromegaly. This may be differentiated by its characteristics: (1) Enlargement of the sella turcica. (2) Changes in the calvarium such as thickening, etc. (3) Prognathism. (4) Polyphagia with an increased basal metabolic rate. (5) Overdevelopment of the cancellous tufts and adjacent soft tissues of the terminal phalanges. (6) Elongation of the phalanges.

Osteitis Deformans. This may be differentiated since in this disease there is: (1) No enlargement of the soft parts. (2) Tendency to curving of the tibia and other long bones. (3) Tendency to asymmetrical enlargement. (4) Tendency of the coarse striae to cross each other at sharp angles with broad coarse spaces between the striae, demonstrated by roentgenographic examination of the bones. (5) Thicker and less dense cortex than is normally seen.

Chronic Venous Stasis. This may produce proliferation of the bone so that one may find the same changes in the distal portions of the extremities as noted in some of the aforementioned conditions. Changes in the blood supply have a definite effect on bone growth in that increase in length and breadth of an entire bone is possible, as is sometimes seen with an arteriovenous anastomosis. Proliferation of a portion of a bone is also possible as for example with small lymphangiomata. However, in this case there were no varicose veins or other evident defects in the venous system and there were definite changes in the skin of the face.

Syphilis. Syphilis of the bones is so similar that it must be ruled out by the absence of associated findings. It may be differentiated since: (1) A syphilitic periostitis most often assumes a lace like pattern which is not to be confused with this pachyperiostosis. (2) There is a positive Wassermann reaction in about 70 per cent. (3) There are skin, cardiovascular, or central nervous system findings present. (4) There is usually a history of a primary lesion.

Repeated blood Wassermann, Kline and Kahn tests including a provocative Wassermann were consistently negative in our case. There were no associated findings to suggest a syphilitic infection.

DISCUSSION

This patient presents a definite pachyderma which is not characteristic of that found in chronic lymphedema or in cutis verticis gyrata. Clinically the normal lines of cleavage of the skin are only slightly accentuated. Microscopic examination, however, reveals an almost identical picture with the characteristic parakeratosis and focal areas of inflammation as described by Touraine, Solente, and Golé. There is in addition a pachyperiostosis and osteophytosis. There were no biopsies of periosteum or bone performed in the cases previously reported. Our cases cannot, therefore, be compared histologically with them. There is a definite similarity in the bones affected. There is agreement as to the age, sex and general health. The onset and progression were insidious, so that the patient did not particularly notice any change from normal until the joint symptoms appeared.

This case, however, presents several differences. The age of onset was approximately 35 which is somewhat older than that of the reported cases. The finger nails are normal in contour. One of the cardinal features, as described originally by Touraine, Solente, and Golé, is the marked furrowing of the skin. In the three clinical types described, the dominant feature is the skin lesion with variations in the periosteal lesion even to complete absence. The dominant feature in our case is the periosteal lesion with the skin furrowing a less prominent sign.

There is no evident etiological factor of the disease in this patient. One has to consider dysfunction of the endocrine system as a possible cause. The presence of Prolan in the urine might indicate an excessive production of estrogens. What possible effect excessive estrogens in the male have on the calcium metabolism is still a research problem.

In 1938 Gardner and Pfeiffer,[15] and in 1940 Sutro,[16] reported that in the mouse, injections of estradiol benzoate over a long period of time produced marked disturbances in calcium. The pelves showed resorption and the long bones showed an increase in density due to replacement of the bone marrow by bone spicules. Later, Wentworth, Smith and Gardner[17] reported that the continued use of large doses of estradiol benzoate in mice produced in addition, significantly higher concentrations of inorganic substances in the femurs and pelves than in control mice, or mice receiving testosterone propionate, or estradiol benzoate plus testosterone propionate.

In our case the bone marrow was not involved as far as roentgenographic studies could determine. There was, however, evidence of resorption in part of the skeletal structure and excessive calcification in others.

It is interesting to note that where these bone changes were produced experimentally with estradiol benzoate, a regression could not be secured with testosterone propionate therapy. Androgenic therapy was ineffective in our patient.

Infection may also play a rôle in the production of this syndrome. Our patient had evidence of chronic infection in the teeth and prostate. (Eight abscessed teeth were removed during this observation period.) The increased sedimentation rate may be an indication of such a process or may be due to the process itself. The sudden occurrence of a spontaneous lymphangitis in the right arm would point to the possibility of a chronic streptococcus infection.

CONCLUSION

1. A case of pachydermatitis with pachyperiostosis of the extremities (Touraine-Dolente-Golé syndrome) is presented with a differential diagnosis.

2. The presence of an excessive amount of estrogens in the male is suggested as a possible etiological factor of the syndrome in this patient.

BIBLIOGRAPHY

1. Labbé, M., and Renault, P.: Hypertrophic osteodermopathy, Bull. et mém. Soc. méd. d. hôp. de Par., 1926, 1, 1065–1067.
2. Gronberg, A.: Is cutis verticis gyrata a symptom in an endocrine syndrome which has so far received little attention?   Acta med. Scandinav., 1927, lxvii, 24–42.
3. Touraine, A., Solente, G., and Golé, L.: Un syndrome osteodermopathique: la pachyderme plicaturé avec pachyperiostose des extremites, Presse méd., 1935, xliii, 1820–1824.
4. Meilberger, M.: Über elephantiatische Lidveränderungen zugleich ein Beitrag zur Kenntnis des osteodermopathischen Syndrome Touraine-Solente-Golé, Basel Theses, 1936.
5. Roy, J. N.: A propos de la pachyderme plicature avec pachyperiostose des extremites, Presse méd., 1937, xlv, 403–404.
6. Rintelen, F.: Über elephantiatische Lidveränderungen zugleich ein Beitrag zur Kenntnis des osteodermopathischen Syndrome Touraine-Solente-Golé, Ztschr. f. Augenheilk., 1937, xcii, 1.
7. Giomo, F.: Su di un caso di pachydermia con pachyperiostosi della estremita, Minerva Med., 1937, i, 577.
8. Bamberger, E.: Über Knochenveränderungen bei chronischen Lungen und Herz-Krankheiten, Ztschr. f. klin. Med., 1890, xviii, 183.
9. Marie, P.: del'osteo-arthropathie hypertrophiante pneumonique, Rev. de méd., 1890, x, 1–36.
10. Campbell, D. C., Sacasa, C. F., and Camp, J. D.: Hypertrophic (chronic) osteo-arthropathy, Proc. Staff Meet. Mayo Clin., 1938, xiii, 708–712.
11. Arnold, J.: Acromegalie, Pachyarcrie oder Ostitis, Beitr. z. path. Anat. u. z. allg. Path., 1891, x, 1–8.
12. Oehme, C.: Familiäre akromegalicähnliche Erkrankung besonders des Skellettes, Deutsch. med. Wchnschr., 1919, xlv, 207–209.
13. Muller, W.: Über die familiäre akromegalicähnliche Skeletterkrankung, Beitr. z. klin. Chir., 1930, cl, 616–628.
14. Freund, E.: Idiopathic familial generalized osteophytosis, Am. Jr. Roentgenol., 1938, xxxix, 216–227.
15. Gardner, W. U., and Pfeiffer, C. H.: Skeletal changes in mice receiving estrogens, Proc. Soc. Exper. Biol. and Med., 1938, xxxvii, 678.
16. Sutro, C. J.: Effects of subcutaneous injection of estrogen upon skeleton in immature mice, Proc. Soc. Exper. Biol. and Med., xliv, 151–154.
17. Wentworth, J. H., Smith, P. K., and Gardner, W. U.: The composition of bones of mice receiving estrogens and androgens, Endocrinology, 1940, xxvi, 61–67.

SPONTANEOUS ARTERIOVENOUS COMMUNICATION BE-TWEEN THE AORTA AND SUPERIOR VENA CAVA *

By Lamont R. Schweiger, M.D., Howard B. Burchell, M.D., and Archie H. Baggenstoss, M.D., *Rochester, Minnesota*

Spontaneous communications between the large arteries and veins of the thorax occur with sufficient rarity to warrant a report of the following case.

Case Report

A white woman, aged 45 years, registered at the Mayo Clinic December 16, 1940. She apparently had been well until two years before her registration at the clinic. At that time she had noted that she became fatigued very easily. Approximately one year before she came to the clinic she had noted that dyspnea and palpitation occurred on exertion. Because of the increasing severity of these symptoms in the next six months, she had been forced to curtail her activities and to remain in her home. For six weeks before she came to the clinic her face, neck and anterior and posterior walls of the thorax had been swollen. The face was said to have been more swollen on the left side at the onset, but soon thereafter the right side became more markedly involved. There had been no orthopnea, paroxysmal dyspnea, thoracic pain or peripheral edema. One week after the onset of swelling, a mild infection of the upper part of the respiratory tract had occurred. This infection had aggravated the dyspnea. Two weeks before her arrival at the clinic, the patient had noticed prominent veins in the anterior wall of the thorax. The clinical history disclosed no other significant data.

The significant observations on physical examination were as follows: There was moderate cyanosis of the face, ears and fingers. The face, neck, and thoracic walls were moderately edematous, but there was little swelling of the arms. Numerous dilated superficial veins were observed over the anterior thoracic wall. There was no swelling of the lower extremities. The maximal cardiac impulse was at the midclavicular line, and the heart rate was 100 per minute and regular. The blood pressure was 150 mm. of mercury systolic and 38 mm. diastolic. A continuous loud murmur with systolic accentuation was present over the upper part of the sternum and was heard with greatest intensity at the aortic area. A soft diastolic murmur, seemingly distinct from the first murmur, was heard at the left sternal border. In addition, a continuous thrill with systolic accentuation was palpable over the same area. Pistol-shot sounds were present over the femoral arteries and the peripheral pulse was collapsing in character.

Examination of the eyes revealed normal reflexes and essentially normal visual fields. The fundi exhibited marked fullness of the retinal veins which pulsated strikingly, and there was a definite synchronous pulsation of the retinal arteries. This simultaneous pulsation of both arteries and veins was the striking feature of the funduscopic examination.

A diagnosis of a communication between the ascending aorta and the superior vena cava was made.

The relevant laboratory findings were as follows. The urine, except for albuminuria, grade 2, was normal. The concentration of hemoglobin was 10.6 gm. per 100 c.c. of blood. The erythrocyte and leukocyte counts were 4,240,000 and 5,000 respectively, per cubic millimeter of blood. The following results were obtained with serologic tests for syphilis. The Kline test was 4 plus; Kahn's test was 3 plus; the

Hinton test was positive; and Kolmer's test was very strongly positive. Roentgenologic examination of the thorax revealed dilatation of the supracardiac shadow (figure 1) and enlargement of the cardiac shadow to the left. Roentgenoscopic examination of the thorax revealed a diffuse aneurysmal dilatation of the ascending aorta associated with a diffuse widening of the supracardiac shadow. The electro-

FIG. 1. Increase in width of supracardiac shadow, and cardiac enlargement.

cardiogram was not noteworthy except for right axis deviation (figure 2). The venous pressure, estimated directly, was 52 cm. of water in the right arm and 51 cm. of water in the left arm. There was no distention of the veins of the legs and the venous pressure was not measured in them. The oxygen content, oxygen capacity and oxygen saturation of the arterial and venous blood are shown in table 1.

An attempt was made to demonstrate the collateral circulation and the communication between the aorta and the superior vena cava by injecting 10 c.c. of a

sterile solution (35 per cent, weight/volume) of diodrast (3, 5-diiodo-4-pyridone-N-acetic acid and diethanolamine) into an antecubital vein of each arm simultaneously. This attempt was unsuccessful as only a few collateral channels about the shoulders were visualized.
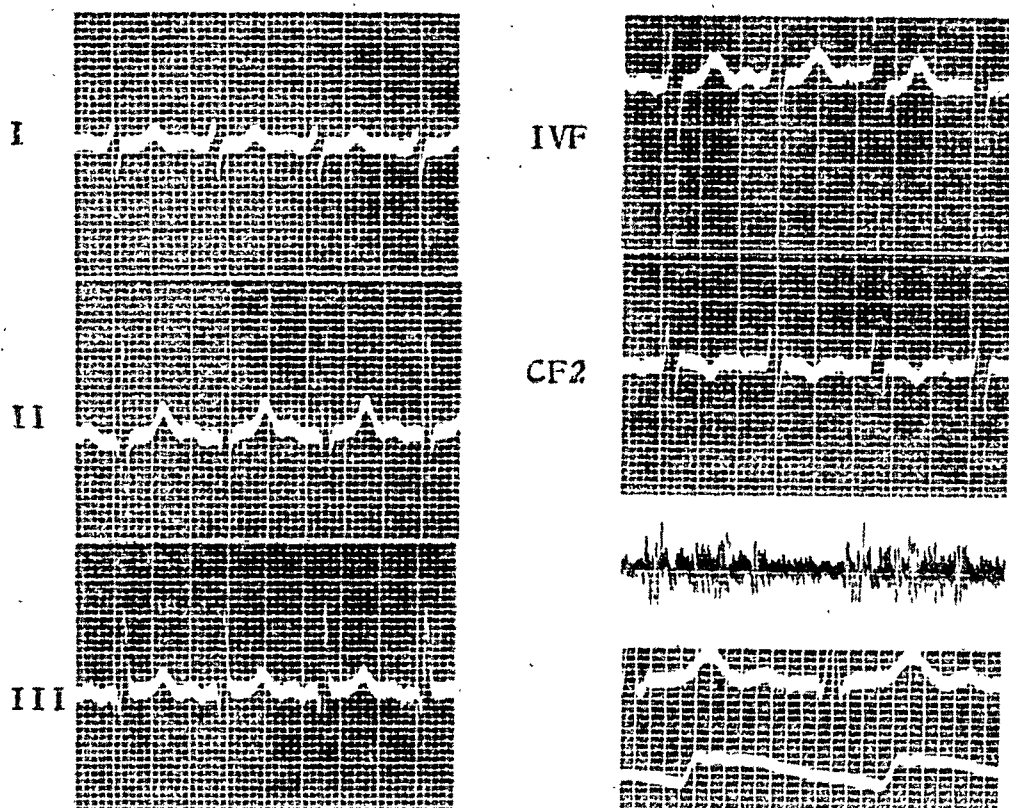
FIG. 2. Electrocardiogram and sound tracing demonstrating moderate right axis deviation and the associated inversion of the T-wave in the CF_2 lead. The recorded murmur is seen to be continuous with systolic accentuation.

During the few weeks following the patient's dismissal from the clinic, there were increasing symptoms and signs of congestive heart failure which terminated in the patient's death approximately one month after leaving the clinic.

Dr. D. O. Manhardt, who performed the necropsy at our request, removed the heart and great vessels en masse and sent them to us for examination. The heart weighed 365 gm. There was a slight amount of fibrinous exudate over the

TABLE I

Oxygen Content, Oxygen Capacity and Oxygen Saturation of Arterial and Venous Blood

Source of Blood	Oxygen Content, c.c. per 100 c.c. of Blood	Oxygen Capacity, c.c. per 100 c.c. of Blood	Oxygen Saturation, Per Cent
Vein of arm	2.68	14.39	18.6
Vein of leg	7.26	14.06	51.6
Femoral artery	12.42	13.86	89.6

right ventricle. The ascending and transverse portions of the aorta were dilated, and a sacculated aneurysm, which measured 8 cm. in its greatest diameter, had originated from the ascending portion. The aneurysm protruded superiorly, posteriorly and to the right (figure 3). The intimal surface was wrinkled and contained longitudinal striations, numerous whitish elevations and some atheromatous plaques. The orifices of the coronary arteries were not appreciably compromised. The portion of the aorta which made up the aneurysm also had the wrinkled appearance associated

FIG. 3. Aneurysm of the ascending aorta associated with saccular protrusions, dilatation of the aortic ring, and cardiac dilatation and hypertrophy.

with syphilitic aortitis. In the posterolateral aspect of the sac, where the greatest thinning had occurred, there were two openings which communicated with the superior vena cava. The larger opening was roughly oval in shape, had a ragged edge and was 5 mm. in its long diameter. It was situated about 7 cm. above the aortic valve. Immediately below this opening was a smaller one which was 2 mm. in diameter.

The superior vena cava was not remarkable except for a moderate degree of dilatation and the presence of a small, flat, mural thrombus in the region of the arteriovenous fistula. Aside from the dilatation and moderate hypertrophy, the heart

was not remarkable except for the appearance of the aortic valve. The cusps were shortened and the edges had a thickened, rolled appearance. The cusps were slightly thickened and there was some separation at the commissures between the right and posterior cusps. The circumference of the aortic ring was 8.5 cm., that of the mitral orifice was 8 cm., that of the tricuspid valve 12 cm. and that of the pulmonic valve ring was 7.5 cm. The left ventricle was 7.5 cm. in depth and the thickness of its wall was 1.5 cm. The right ventricle was 9 cm. in depth and varied between 3 mm. and 7 mm. in thickness. The coronary arteries were freely patent throughout their course although there were a few intimal plaques.

In sections of the ascending and transverse portions of the aorta the most significant abnormalities were the presence of collections of lymphocytes in the media and adventitia, marked destruction of the elastic laminae and scarring by hyaline connective tissue. In the intima there were marked scarring, folding and indentations corresponding to the longitudinal scars noted grossly. There were also a few patches of atherosclerosis and calcification. In the region of the fistulas, the adventitia of the ascending aorta was firmly fused with the wall of the superior vena cava. At the borders of the fistulas, there were patches of necrosis and fibroblastic proliferation. In this region, the aortic wall had become greatly thinned and much of the muscular and elastic tissue had been replaced by hyalinized connective tissue.

In the wall of the superior vena cava there also were collections of lymphocytes, destruction of elastic tissue, and an increase in the amount of fibrous connective tissue. Sections through the edges of the perforations revealed necrosis of the walls and an attached layer of fibrin.

Sections of the descending, thoracic and abdominal portions of the aorta revealed similar but much less striking changes than those in the ascending and transverse portions. Sections of the aortic valve revealed that the cusp had been greatly thickened at the free margin by fibrous connective tissue. Focal regions of fibrosis were found in the myocardium.

The following anatomic diagnoses were made: (1) syphilitic aortitis and aneurysm, (2) arteriovenous fistula (aorta to superior vena cava), (3) chronic syphilitic aortic valvulitis and insufficiency, and (4) hypertrophy of heart (365 gm., calculated normal weight, 288 gm.).

COMMENT

In an analysis of the reported cases of spontaneous communications between the large arteries and veins of the thorax, Armstrong, Coggin and Hendrickson were able to collect 124 cases of this condition up to 1938. Furthermore, these authors said that in more than 19,000 postmortem examinations at the Los Angeles County Hospital, only two cases of this condition had been seen. In the postmortem records of the Mayo Clinic this is the only instance of the condition that has been encountered.

Armstrong, Coggin and Hendrickson, in their analysis of the reported cases, noted that although the incidence of thoracic arteriovenous aneurysm attributed to syphilis was less than 50 per cent, this figure was undoubtedly too low. In support of this premise, they called attention to the fact that 26 cases have been collected since 1925 and in 20 of these cases there was definite evidence of syphilis. Moreover, in two of the 26 cases necropsy had not been performed and the clinical records were unavailable in one case. Thus, excluding these three cases, there was positive evidence of syphilis in 87 per cent of the cases.

The characteristic signs of an arteriovenous communication were present in the case which we have reported. During the 10-day period the patient was

under our observation, the pulse rate was consistently elevated, the pulse pressure remained high, and the characteristic continuous murmur and thrill, with systolic accentuation, were noted. The venous pressure in the legs apparently was not elevated and this is in agreement with other observations of a normal venous pressure in that part of the circulation not directly involved in the abnormal communication. The marked elevation of the venous pressure in the upper extremities was interpreted to be due to the passage of blood, under arterial pressure, into the vena cava although partial obstruction of the superior vena cava by pressure of the contiguous aneurysm may have played a part. The failure of diodrast, injected simultaneously into both antecubital veins, to be demonstrable in the superior vena cava on roentgenoscopic examination is taken as further evidence for this conclusion. The pronounced oxygen desaturation of the venous blood in the upper extremities when compared with that for the lower extremities was again an important finding that was consistent with the lesion.

In the postmortem findings it is to be noted that the heart was dilated but not greatly hypertrophied, as judged by its weight. The absence of prominent cardiac hypertrophy together with right axis deviation in the electrocardiogram gives us some reason to believe that the terminal cardiac failure and dilatation might have been due mainly to the arteriovenous communication. The onset of swelling of the face, neck, and walls of the thorax approximately six weeks before the patient appeared at the clinic, and the fact that the patient died one month after her dismissal from the clinic, probably indicate that the communication between the aorta and superior vena cava had been present for approximately three months. We should like to emphasize the long survival time after the development of the communications between the aorta and the superior vena cava.

SUMMARY

In the case of abnormal communication between the aorta and superior vena cava that we have just reported the characteristic signs of an arteriovenous fistula in the thorax were present. Attention is directed to the relatively long duration of life after the establishment of the communication.

BIBLIOGRAPHY

1. ARMSTRONG, E. L., COGGIN, C. B., and HENDRICKSON, H. S.: Spontaneous arteriovenous aneurysms of the thorax: a review of the literature, with a report of two cases, Arch. Int. Med., 1939, lxiii, 298–317.

EDITORIAL

THE WAR AND MEDICAL EDUCATION. II

ONE year ago this column [1] was devoted to a discussion of the various problems in medical education that had arisen as a result of the war. At that time, the majority of medical schools in this country had already adopted an accelerated program with the admission of a new class every nine months and continuous instruction the year around, thus making it possible for the medical student to obtain the degree of Doctor of Medicine in three calendar years.

As potential disadvantages of this accelerated program, it was pointed out that the students—not to mention the depleted and overworked faculties —might grow stale under the pressure of such an intensified schedule and that many of the students might find the increased financial burden a difficult hurdle to surmount. Undoubtedly all medical students have felt the strain of uninterrupted concentrated study; a few are frank to admit that they have "grown stale" and are not deriving full benefit from their courses. Moreover, neither the decrease in weight nor the increase in furrows among the professors and instructors can be attributed solely to food-rationing. But on the whole, the accelerated program has worked out very well to date and more than justified its adoption in the number of new medical officers that are soon to be rendered available for active duty with the armed forces. The financial problem has been completely eliminated for the majority of medical students since the inauguration of the Army and Navy training programs.

Late in 1942, the draft age limit was lowered to 18 years. It was obvious that new legislation would be necessary to insure an adequate supply of qualified premedical students to fill the classes entering the medical schools every nine months. The answer to this problem was soon to come with the creation of the Army Specialized Training Program (A.S.T.P.) and the Navy College Training Program (V–12). These programs permitted medical and premedical students to enlist in the reserve corps of the army or navy and to carry on their studies while under the jurisdiction of military officials.

For the time being, training in medicine under the A.S.T.P. is limited to enlisted men currently in attendance at approved medical schools and enlisted men who have been accepted for future entering classes by medical schools that are participating in the A.S.T.P. In other words, any enlisted man in the army who has passed the qualifying tests for the A.S.T.P. may apply for admission to the medical school of his choice anywhere in the country and, if accepted, he will be assigned to an A.S.T.P. college unit to complete his premedical training at the government's expense before entering medical school. Civilian students who have completed their premedical

[1] The war and medical education, Editorial, ANN. INT. MED., 1942, xvii, 874–876.

training under a 2–A selective service classification and have been accepted by an approved medical school may apply to their draft boards for voluntary induction with the request that they be assigned to the A.S.T.P. unit at that medical school. The army has honored such requests for assignment to classes entering affiliated medical schools in 1943 and 1944.

At the present writing, the Navy V–12 Program for *premedical* students is further advanced than the Army Specialized Training Program. The Navy has established V–12 units for premedical training at several colleges in each naval district. A student in such a V–12 unit who was admitted to an affiliated medical school prior to July 1, 1943 will be permitted to attend that medical school, provided he has been admitted to the first entering class for which he is eligible after the completion of his premedical course. All other V–12 premedical students must apply for admission to medical school through the commanding officer of their unit. They are allowed to specify their first, second, and third choice medical schools on their application, but the majority will probably be assigned to medical schools with V–12 units located in the same naval district. A board of deans has been set up in each naval district to assist the Navy in selecting from the V–12 college units students who seem qualified for the study of medicine and in assigning these students to medical schools. It seems likely that the Army will set up a similar system for assigning premedical students in the A.S.T.P. to classes enrolling in medical schools in 1945.

So much for the army and navy programs as they apply to premedical students. Early last summer the majority of *medical students* who were physically acceptable for military service enlisted in either the A.S.T.P. or the Navy V–12 program. Those students who already held reserve commissions (on an inactive status) of second lieutenant in the Medical Administrative Corps of the Army or ensign (HVP) in the Navy were granted the option of resigning their commissions in order to join the Enlisted Reserve of their respective services. All enlistees were formally inducted into the army or navy, issued uniforms, and designated cadets with the pay and maintenance allowance of a private in the army or an apprentice seaman in the navy. The army cadets wear the uniform of a private whereas the navy cadets are attired in uniforms similar to those worn by the midshipmen at Annapolis. The students in both enlisted reserve corps are subject to military discipline with a certain number of hours of military training and instruction every week, but it is commendable that in general the military authorities have made every effort to interfere as little as possible with the medical curriculum. The scientific instruction and administration of the medical schools is left entirely in the hands of the faculty and administrative officials of the schools who retain full power to drop a student for academic failures. If a cadet fails any of his courses, the failure must be reported to his commanding officer who in turn may at his discretion recommend that the cadet be separated from his medical unit and assigned to some other

branch of the service. Furthermore, the commanding officer may at any time separate a cadet from his unit for "behavior unbecoming to an officer." The Army and Navy have contracted with the medical schools to defray the tuition of the cadets and to furnish the cadets with most of the technical equipment and textbooks that they require for their medical course. On the other hand, those students who elected to keep their reserve commissions (2nd Lieutenant in the Medical Administrative Corps or Ensign HVP) remain on an inactive status in civilian attire and must defray all the expenses of medical school and maintenance out of their own pockets. The financial advantage to the students of resigning these commissions and joining the enlisted reserve is obvious.

The internship-residency system has always occupied a most important place in basic postgraduate education of newly graduated physicians. The hospitals of the United States with the approval of Procurement and Assignment Service have recently adopted the nine-nine-nine month plan [2] for the allocation of interns and residents in 1944. This plan involves three major changes: (1) internships and residencies are being changed over from a twelve to a nine month base period to remedy the difficulties inherent in a nine month medical school year and a twelve month hospital year; (2) certain essential commissioned men will be permitted to give some service as hospital residents instead of being ordered to active duty immediately upon the completion of their internships; (3) interns as well as residents are included in the allocation plan. This proposal has been conditionally accepted by the Surgeons General of the Army and Navy in the following form: (1) the internship shall be reduced to nine months; (2) one third of the interns who hold commissions in the Army and Navy may be deferred for nine months (tenth to eighteenth months) as assistant residents; (3) one-half of this number or one-sixth of the total number of commissioned interns may be deferred for an additional nine months (nineteenth to twenty-seventh months) as residents. Under this plan, two-thirds of all commissioned interns now in hospitals will be eligible for orders to active duty on or about January 1, 1944 and at about the time the new graduates will begin their internships. The Procurement and Assignment Service believes that minimum adequate hospital medical service can be provided only if each hospital exerts every effort to obtain and retain women and physically disqualified house officers, since the number of men to be deferred by the armed services will not be adequate to meet even the minimal needs for hospital residents. The overall cut will be about one-third. For the average hospital the allocation for 1944 will be somewhat less than two-thirds of the 1940 number of residents and two-thirds to three-fourths the 1940 number of interns. Such a curtailment of hospital staffs is bound to lower the quality of service that the hospital will be able to render patients as well as to deprive the house officers themselves

[2] Plan for the allocation of interns and residents in hospitals, 1944, Jr. Am. Med. Assoc., 1943, cxxiii, 98.

of the more thorough training that was available to them in the past. However, it seems to be the best solution that can be offered under current wartime conditions, and it is to be hoped that these young men will be afforded the opportunity for further service in hospitals during the post-war period.

Lastly, an extensive program for postgraduate medical instruction, especially designed for medical officers on active duty at the present time, has been developed by the Central Committee of the Wartime Graduate Medical Meetings. The national consultants have compiled the names of prominent men throughout the entire country who will serve on a national faculty. This faculty will assist the regional committees in meeting the demands for teachers. The American College of Physicians may take just pride in the fact that it anticipated the need for just such postgraduate instruction and indeed organized a number of such regional meetings early in 1943.

It is gratifying to record that our system of medical education has proved sufficiently flexible to meet the various exigencies occasioned by the war and to adjust itself so smoothly to the radical changes which we have briefly outlined.

W. H. B.

REVIEWS

Neurology. By Roy R. Grinker, M.D. Third Edition. 1136 pages; 26 × 17 cm. Charles C. Thomas, Springfield, Illinois. 1943. Price, $6.50.

This third revision of an already familiar and accepted textbook evidences a complete re-reading and appraisal not only of fact but of the manner in which it is presented. In both respects, welcome changes have been made.

In previous editions the chapters covering the anatomy and physiology of the nervous system were largely separate from those dealing with clinical data. Insofar as is possible, these fundamental data have now been incorporated with the clinical material. This regrouping has been of great help.

Much has been added, particularly concerning the chemistry of the brain. The discussion of epilepsy has been amplified through the inclusion of electroencephalographic data. A delightful chapter on cerebral neoplasms, contributed by Paul C. Bucy, entirely replaces the previous treatment of this subject.

Re-writing of much text with deletion of occasional needless words or phrases and the consistent omission of all controversial material has made the volume even more concise than before. In the treatment of the "newer" diseases, such as ruptured intervertebral disc, a conservative approach is taken. Continued emphasis of the pathogenesis is seen. There is a substantial increase in the number of tables and illustrations, many of which are either original or have been taken from most reliable sources. The bibliography of each chapter has been revised and augmented by many new references.

The value of this textbook as a basic reference for student and practitioner has been definitely increased by virtue of this revision.

J. A. W.

Vitamins and Hormones. *Vol. I.* *Advances in Research and.Applications.* Edited by Robert S. Harris and Kenneth V. Thimann. With a Foreword by E. V. McCollum. 452 pages; 23.5 × 15.5 cm. Academic Press, Inc., New York City. 1943. Price, $6.50.

This volume begins a new review series designed to correlate various aspects of research in the field of vitamins and hormones. No attempt has been made to cover the entire field, but ten subjects are rather exhaustively treated by well qualified investigators. The chapter titles include the following: Choline-Chemistry and Significance as a Dietary Factor, The Appraisal of Nutritional States, Physical Methods for the Identification and Assay of Vitamins and Hormones, The Chemistry and Physiological Relationship between Vitamins and Amino Acids, The Photoceptor Function of the Carotenoids and Vitamin A, The Significance of the Vitamin Content of Tissues, Growth-Factor for Protozoa, Physiology of Anti-Pernicious Anemia Material, The Intermediate Metabolism of the Sex Hormones, and The Hormones of the Adrenal Cortex. Each chapter is carefully outlined both in the table of contents and at the beginning of the chapter, thus facilitating reference to subtopics. Extensive references appear at the end of each chapter, and there is an author and subject index.

This series should become more and more valuable as a comprehensive reference with each succeeding annual volume.

M. A. A.

BOOKS RECEIVED

Books received during October are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Clinical Diagnosis by Laboratory Examinations. By JOHN A. KOLMER, M.S., M.D., Dr.P.H., Sc.D., LL.D., L.H.D., F.A.C.P. 1239 pages; 25 × 17.5 cm. 1943. D. Appleton-Century Company, Inc., New York. Price, $8.00.

A Clinical and Experimental Investigation of the Blood Cholesterol Content in Myxoedema and Other Conditions. By E. H. STOKES, M.B., Ch.M. (Sydney), F.R.A.C.P. 121 pages; 25 × 18.5 cm. 1941. Australasian Medical Publishing Company Limited, Sydney, Australia. (Accepted as a thesis for admission to the degree of Doctor of Medicine in the University of Sydney.) ·

Renewal Pages—Specialties in Medical Practice. Edited by EDGAR VAN NUYS ALLEN, M.D. 270 pages; 24.5 × 18.5. 1943. Thomas Nelson and Sons, New York. Price, $5.40 per set.

Biological Symposia. Volume X: Frontiers in Cytochemistry. Edited by JAQUES CATTELL. 334 pages; 25 × 17.5 cm. 1943. Jaques Cattell Press, Lancaster, Pennsylvania. Price, $3.50.

Peripheral Vascular Diseases (Angiology). By SAUL S. SAMUELS, A.M., M.D. 84 pages; 22 × 14.5 cm. 1943. Oxford University Press, New York. Price, $2.00.

Proctology. By SYLVAN D. MANHEIM, M.D. 137 pages; 22 × 14.5 cm. 1943. Oxford University Press, New York. Price, $2.00.

China's Health Problems. By DR. SZEMING SZE (General Secretary, Chinese Medical Association; Editor, Chinese Medical Journal). 60 pages; 23.5 × 16 cm. 1943. Chinese Medical Association, Washington, D. C. Price, $1.00.

Anales del Instituto de Medicina Experimental de Valencia. Tomo 1. Fasciculo 1. 237 pages; 21 × 15.5 cm. 1943. Editorial F. Domenech, S.A., Valencia.

Irrigacion Normal del Nodulo de Keith y Flack, Tawara, Haz de His y Sus Ramas. Estudio Previo de la Distribucion de los Gruesos Vasos Coronarios Cardiacos. By DR. EDUARDO F. LASCANO. 100 pages; 27 × 18.5 cm. 1942. El Ateneo, Buenos Aires, Argentina.

The Medical Use of Sulphonamides. Medical Research Council—War Memorandum No. 10. 46 pages; 24.5 × 15.5 cm. 1943. His Majesty's Stationery Office, London, England. Price, 9d. net.

Manometric Methods as Applied to the Measurement of Cell Respiration and Other Processes. 2nd Edition. By MALCOLM DIXON, Ph.D., Sc.D., F.R.S. With a Foreword by SIR F. G. HOPKINS, O.M., F.R.S. 157 pages; 19.5 × 13.5 cm. 1943. The Macmillan Company, New York City. Price, $1.75.

COLLEGE NEWS NOTES

The College is gratified to announce that Dr. Emry G. Hyatt, F.A.C.P., Tulsa, Okla., and Dr. Raymond Sands, F.A.C.P., Santa Monica, Calif., became Life Members of the American College of Physicians on November 23, 1943, having subscribed the amount designated in the By-laws, said payments having been added to the permanent Endowment Fund of the College.

GIFTS TO THE COLLEGE LIBRARY

We gratefully acknowledge receipt of the following gifts to the College Library of Publications by Members:

Books

Dr. Alexander S. Wiener (Associate), Brooklyn, N. Y.—"Blood Groups and Transfusion."

Reprints

J. Heinz Ahronheim (Associate), Captain, (MC), AUS—1 reprint;
Dr. Frank N. Allan, F.A.C.P., Boston, Mass.—1 reprint;
Dr. Russell S. Anderson, F.A.C.P., Erie, Pa.—1 reprint;
Dr. Arthur J. Atkinson (Associate), Chicago, Ill.—8 reprints;
Dr. Andrew L. Banyai, F.A.C.P., Wauwatosa, Wis.—2 reprints;
H. Dumont Clark (Associate), Major, (MC), AUS—1 reprint;
Dr. Oscar G. Costa-Mandry, F.A.C.P., Santurce, San Juan, P. R.—1 reprint;
Daniel B. Faust, F.A.C.P., Colonel, (MC), U. S. Army—1 reprint;
Harold J. Harris, F.A.C.P., Lieutenant Commander, (MC), U. S. Naval Reserve— 1 reprint;
Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa.—2 reprints;
Dr. Arthur B. Landry, F.A.C.P., Hartford, Conn.—1 reprint;
Charles S. Mudgett, F.A.C.P., Colonel, (MC), U. S. Army—1 reprint;
Dr. Foster Murray, F.A.C.P., Brooklyn, N. Y.—1 reprint;
Dr. Franklin B. Peck, F.A.C.P., Indianapolis, Ind.—2 reprints;
Dr. Earle W. Phillips, F.A.C.P., Phoenix, Ariz.—2 reprints;
Walter L. Voegtlin (Associate), Lieutenant Commander, (MC), U. S. Naval Reserve 1 reprint;
Charles E. Watts, F.A.C.P., Captain, (MC), U. S. Naval Reserve—1 reprint;
Dr. Alexander S. Wiener (Associate), Brooklyn, N. Y.—7 reprints;
Dr. Salvador Zubiran, F.A.C.P., Mexico City, D. F.—2 reprints.

ADDITIONAL A. C. P. MEMBERS IN THE ARMED FORCES

Already published in preceding issues of this journal were the names of 1,489 Fellows and Associates of the College on active military duty. Herewith are reported the names of 12 additional members, bringing the grand total to 1,501.

M. Meredith Baumgartner	Alphonse McMahon
William C. Dine	Gilberto S. Pesquera
Thomas H. Ham	Albert Soiland
George J. Kastlin	Arthur S. Strauss
Leslie R. Kober	George W. Weber
Robert P. McCombs	G. Stuart Wilson

The following members of the American College of Physicians have either retired or have been honorably discharged for physical disability from active service in the armed forces:

Major W. Osler Abbott, (MC), AUS, Philadelphia, Pa.—discharged, 9/28/42; deceased, 9/10/43.

Lieutenant Commander Douglas D. Baugh, (MC), USN, Columbus, Miss.—discharged, 12/18/42.

Captain Michael Bernreiter, (MC), AUS, Kansas City, Mo.—discharged, 7/11/43.

Lieutenant (jg) George A. Cann, (MC), USNR, Reno, Nev.—retired, 4/20/43.

Lieutenant Colonel Harold Archibald DesBrisay, RCAMC, Vancouver, B. C., Can.—discharged, October, 1942.

Captain Paul D. Foster, (MC), AUS, Los Angeles, Calif.—discharged, 2/3/43.

Lieutenant Colonel Ben R. Heninger, (MC), AUS, New Orleans, La.—discharged, 1/31/43.

Lieutenant Commander James J. Hennessy, (MC), USNR, Hartford, Conn.—discharged, 4/10/43.

Major Edwin P. Kolb, (MC), AUS, Holtsville, N. Y.—retired, 11/6/42.

Captain Milton M. Portis, (MC), California State Guard, Beverly Hills, Calif.—retired to inactive list, 4/15/43.

Captain H. Milton Rogers, (MC), AUS, St. Petersburg, Fla.—discharged, 10/15/43.

Lieutenant Colonel James F. Rooney, (MC), AUS, Albany, N. Y.—discharged, 5/28/41.

Lieutenant Commander Ralph L. Shanno, (MC), USNR, Forty Fort, Pa.—discharged, 11/1/42.

Lieutenant Commander Walter C. Smallwood, (MC), USNR, Long Beach, Calif.—discharged, 5/15/42.

Edwin E. Ziegler, U. S. Public Health Service, Bethlehem, Pa.—resigned, 9/8/42.

New College Membership Roster

In accordance with directions of the Executive Committee of the Board of Regents, the American College of Physicians has forgone the publication of a complete membership directory for 1943, but it has published a full "Membership Roster," which includes the listing of Associates, Fellows and Masters as of August, 1943. This publication was mailed to all members in good standing early in November, with the exception of those members who are on overseas military service. A copy will be held for such members, subject to delivery at their request.

Next Examinations, American Board of Internal Medicine

The next written examination of the American Board of Internal Medicine will be held February 21, 1944. The Assistant Secretary-Treasurer, Dr. William A. Werrell, 1301 University Ave., Madison 5, Wis., announced that applications for admission to the examination should be filed early in December, before December 15, if possible. More leeway will be granted to candidates on military duty and a special effort will be made to accommodate them at the examinations.

Announcement, Directory of Medical Specialists

The Directory of Medical Specialists will be published by the A. N. Marquis Company of Chicago, publishers of "Who's Who in America." Previous editions

were published by the Columbia University Press of New York City. The next edition will appear in 1945, but supplemental lists of those certified by American Boards since the last edition of the Directory, 1942, will be published.

Dr. Paul Titus of Pittsburgh will continue as the Directing Editor and Dr. J. Stewart Rodman of Philadelphia will continue as Associate Editor. The Editorial Board is composed of the Secretaries of the fifteen American Boards. Communications should be addressed to the Directing Editor, Directory of Medical Specialists, 919 N. Michigan Ave., Chicago 11, Ill.

Dr. Parley Nelson (Associate), Rexburg, Idaho, has been elected President of the Idaho State Medical Association for the coming year.

Captain Norman L. Murray (Associate), (MC), AUS, stationed with the Air Force at Gowen Field, Boise, Idaho, addressed the Southwestern Idaho District Medical Society on October 21, 1943. His subject was "Office Management of the Diabetic." Captain Murray is formerly of New Jersey.

Dr. Howard Wakefield, F.A.C.P., Chicago, Ill., spoke on "Acute and Chronic Coronary Occlusion" at a meeting of the Du Page County Medical Society in Elmhurst, Ill., on November 17, 1943.

Dr. Walter E. Macpherson (Associate), of Los Angeles, Calif., is the President of the College of Medical Evangelists.

On November 10, 1943, Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Chairman of the Committee on Nutrition of the Medical Society of the State of Pennsylvania, addressed the First Regional Pennsylvania Health Institute, Erie, Pa., on the subject, "Improving Nutrition of all the People." The meeting was held under the auspices of the Pennsylvania State Department of Health.

Dr. Frank N. Allan, F.A.C.P., Boston, Mass., addressed a District Meeting of the Ontario Medical Society in Brantford, Ont., Can., on October 6, 1943. His subject was "Why Do People Feel Weak and Tired? Differential Diagnosis and Treatment."

Dr. Edward J. Stieglitz, F.A.C.P., Washington, D. C. addressed the 8th Annual Meeting of the Industrial Hygiene Foundation at Pittsburgh, November 11, on "Health Problems of the Older Employee and Employer."

Dr. George E. Baker, F.A.C.P., Casper, Wyo., delivered an address on "Rocky Mountain Spotted Fever; an Increasing Hazard: Diagnosis and Treatment," before the Chicago meeting of the Inter-State Post Graduate Medical Association of North America, October 26, 1943.

AMERICAN MEDICAL ASSOCIATION TO RESUME ANNUAL SESSIONS

The Journal of the American Medical Association in a recent issue announced that its annual session will be held in Chicago, June 12–16, 1944. The meetings of the House of Delegates will be held at the Palmer House and the scientific exhibit will be installed there. However, the technical exhibit will be housed at the Stevens Hotel.

WISCONSIN STATE MEDICAL SOCIETY ANNOUNCES DATES FOR ANNUAL MEETING

The State Medical Society of Wisconsin will hold its 1944 session September 18–20 in Milwaukee. The above announcement is made in an effort to encourage other societies to avoid conflicts in meeting dates.

COURSE IN HOSPITAL ADMINISTRATION

Northwestern University, Chicago, through a grant received from the Johnson & Johnson Research Foundation, has initiated a course in hospital administration with an enrollment of thirty-nine students, only eight of whom who are not connected with a hospital. Of the eight persons not associated with a hospital, two are employed on hospital magazines, two are physicians, one is director of a hospital council and one is employed by the American College of Surgeons.

WESTERN RESERVE UNIVERSITY SCHOOL OF MEDICINE CELEBRATES ITS ONE HUNDREDTH ANNIVERSARY

Western Reserve University School of Medicine, Cleveland, Ohio, celebrated its One Hundredth Anniversary, October 27, 1943. Dr. Howard T. Karsner, F.A.C.P., Cleveland, was the official representative of the American College of Physicians on this occasion.

At 11:30 a.m., Dr. George H. Whipple addressed an audience of about 600 on the subject of "Blood Plasma Proteins—Their Production, Function, Substitution and Replacement." He outlined with great clarity the progress that has been made in the scientific study of the utilization of amino acids and of whole plasma in connection with the building of hemoglobin and the liberation of proteins into the circulation. Immediately following, a luncheon was given by the University to delegates to the celebration, delegates to the Association of American Medical Colleges, and guest speakers of the celebration and of the meetings of the Association. At 3:30 p.m., the University Convocation was attended by about 150 delegates from universities, colleges, medical societies and philanthropic foundations. A guard of honor was

formed by medical students representing both Army and Navy. President W. G. Leutner presided, and addresses were delivered by Dr. Howard T. Karsner and Dr. Alan Gregg of the Rockefeller Foundation. Dr. Gregg's address, "The Matrix of Medicine," was a scholarly approach to the situation of Medicine in relation to educational, cultural and other matrices in which Medicine finds itself. He suggested that a non-political national committee be organized to make recommendations concerning the future of medical practice and education. In the evening a dinner was given by the University, attended by delegates, members of the faculties and alumni. About 400 were present and were addressed by Dr. Reginald Fitz of the Harvard Medical School. The title of his address, "The Crimson Thread," was developed so that the various interchanges of ideas and of personnel between the School of Medicine in Cleveland and the Harvard Medical School were brought out in interesting and entertaining fashion.

On the morning of the following day, scientific addresses were made to the alumni by graduates of the School who have attained distinction in various parts of the country. The Commencement for the Medical School was held in the afternoon and in the evening the principal address at the Alumni dinner was by Frederick C. Waite, Emeritus Professor of Histology and Embryology, who showed clearly the influence of the School on various community activities.

REPORT ON REGIONAL MEETING IN SEATTLE

The first Regional Meeting of the American College of Physicians to be held in the Northwest was conducted at Seattle, Washington, Friday, September 24, 1943, and included the territory of Washington, Oregon, Idaho, Alberta, British Columbia, Manitoba and Saskatchewan. The meeting was eminently successful; the program was superior and the attendance was greater than anticipated. The medical population in that area is not nearly so dense as in many other parts in this country and Canada, and consequently the number of members of the College is small in comparison with more densely populated areas. Fifty per cent of all College Fellows and Associates were in attendance, a percentage not yet reached by any other area of the country at a Regional Meeting. In addition, there were 92 guests including 14 officers from the Royal Canadian Army Medical Corps, 2 officers from the Royal Canadian Navy Medical Corps, 34 officers from the U. S. Army Medical Corps, 18 officers from the U. S. Navy Medical Corps, 2 officers from the U. S. Public Health Service and 22 civilian physicians.

Dr. Edwin G. Bannick, Acting Governor for Washington, was the General Chairman, and was ably assisted by Dr. Homer P. Rush, College Governor for Oregon; Dr. Samuel M. Poindexter, Acting Governor for Idaho; and Dr. George F. Strong of Vancouver, Governor for the Southwestern Provinces of Canada. These Governors in turn were ably aided by active committees in each state and province.

REPORT ON REGIONAL MEETING IN CHICAGO

A Regional Meeting of the College for Illinois, Indiana, Iowa, Michigan and Wisconsin was held at the Drake Hotel, Chicago, Saturday, October 16, 1943, under the General Chairmanship of Dr. LeRoy H. Sloan, Governor for Northern Illinois, and the active participation of Dr. Cecil M. Jack of Decatur, Governor for Southern Illinois; Dr. Robert M. Moore, Governor for Indiana; Dr. B. F. Wolverton of Cedar Rapids, Governor for Iowa; Dr. P. L. Ledwidge of Detroit, Acting Governor for Michigan; and Dr. Elmer L. Sevringhaus of Madison, Governor for Wisconsin.

This Regional Meeting concluded a week devoted to a postgraduate course in Endocrinology under the auspices of the College at the Presbyterian Hospital, directed by Dr. Willard O. Thompson. In this course, there were registered 78 different physicians, mostly Fellows and Associates of the College and Medical Officers of the Armed Forces. No activity ever conducted by the College received more expressions of appreciation and commendation than this course.

On Friday evening, October 15, the entire group from the Postgraduate Course, with a faculty selected by the College and by the Committee on War-Time Graduate Medical Meetings, went to the Great Lakes Naval Hospital where a program of postgraduate lectures was presented to Medical Officers at that station and other Medical Officers from Army installations from the surrounding territory. About 250 were in attendance.

The official Regional Meeting of the College followed on Saturday, October 16 at the Drake Hotel in Chicago. The program has already been published in a previous issue of this journal. There were 222 members of the College in attendance, or 36.3 per cent of the members from the territory represented. In addition, there were 130 guests, including 64 Medical Officers from the Army and Navy and Public Health Service and 66 non-member civilian physicians. The session was concluded with a dinner meeting in the evening at which approximately 300 were in attendance. The dinner meeting speakers included Dr. Charles H. Cocke, Asheville, N. C., First Vice President of the College; Dr. Ernest E. Irons, Chicago, Ill., President-Elect of the College; Brigadier General Hugh J. Morgan, (MC) U. S. A., Washington, D. C.; Dr. Willard O. Thompson, Chicago, Ill.; and Mr. E. R. Loveland, Philadelphia, Pa., Executive Secretary. Governor Sloan was the Toastmaster.

A. C. P. FELLOWS HONORED AT MEETING OF ASSOCIATION OF MILITARY SURGEONS

At the annual dinner of the Association of Military Surgeons of the United States at Philadelphia, October 22, 1943, Navy Night, the Gorgas Medal was awarded to Dr. Hugh S. Cumming, F.A.C.P., former Surgeon General of the U. S. Public Health Service. This award was founded by John Wyeth & Brother. Captain Louis H. Roddis, F.A.C.P., (MC), U. S. Navy, was awarded the Wellcome Medal, established by Sir Henry Wellcome.

A. C. P. REGIONAL MEETING HELD IN PHILADELPHIA

A Regional Meeting of the American College of Physicians for Eastern Pennsylvania, Delaware, New Jersey and Eastern New York was held in Philadelphia, November 19, 1943, under the Chairmanship of Dr. Edward L. Bortz (Commander, MC, U. S. N. R.), Governor for Eastern Pennsylvania, and the active participation of the College Governors for the territory, namely; Dr. Lewis B. Flinn, Governor for Delaware; Dr. George H. Lathrope, Governor for New Jersey; and Dr. Asa L. Lincoln, Governor for Eastern New York. The Regional Meeting program terminated a two-weeks postgraduate course in Special Medicine, conducted by the College for its members and for medical officers in the armed forces, at Philadelphia Institutions under the Directorship of Dr. Charles L. Brown, F.A.C.P., Professor of Medicine at Temple University.

An analysis of the attendance at the Regional Meeting appears below. This probably was one of the largest Regional Meetings the College has held and it was the consensus that this meeting was one of the best in the College history.

A. By geographical distribution:

	% of Membership	Members	Guests	Total
Eastern Pennsylvania	42.5	113	80	193
Delaware	41.6	5	4	9
New Jersey	27.1	31	20	51
Eastern New York	6.2	40	8	48
Other States		64	15	79
Canada		3	1	4
		256	128	384

B. By class:

Fellows	Associates	Guests	Total	RCAMC	(MC)USA
192	64	128	384	3	52

(MC)USN	USPHS	Civilian
21	6	302

25% of the A. C. P. members in the territory of this Regional Meeting was in attendance.

The program was as follows:

MORNING SESSION—9:30 a.m.

Hospital of the University of Pennsylvania

Presiding Officer

O. H. PERRY PEPPER, M.D., F.A.C.P.

9:30 "Hypoprothrombinemia."
    DR. FRANKLIN D. MURPHY.
9:45 "Differentiation of Functional Hypoglycemia from That Due to Adenoma of the Pancreas."
    DR. FRANCIS D. W. LUKENS.
10:00 "Case of Toxoplasmic Encephalomyelitis."
    DR. JAMES WENDELL.
10:15 "Statistics on Medical Treatment of Bleeding Ulcer."
    DR. T. GRIER MILLER.
10:30 "Demonstration of a Small Oxygen Tent."
    DR. LINCOLN GODFREY, JR.
10:40 "The Case for Trial of Castration in Diffuse Lupus Erythematosis."
    DR. EDWARD ROSE.
11:00 "Gelatin as a Blood Substitute."
    DR. C. EVERETT KOOP.
11:15 "The Virus Encephalitides."
    DR. GEORGE D. GAMMON.
11:35 "Comments on Hemoglobinuria."
    DR. WILLIAM C. STADIE.
11:45 "Electrocardiographic Interpretation."
    DR. CHARLES C. WOLFERTH.

LUNCHEON
12:30 p.m.

COLLEGE HEADQUARTERS
4200 Pine Street, Philadelphia, Pa.

AFTERNOON SESSION—3:00 p.m.

Ballroom, Benjamin Franklin Hotel

Presiding Officer

GEORGE H. LATHROPE, M.D., F.A.C.P.

Governor for New Jersey

1. "Medicine Overseas."

HUGH J. MORGAN, M.D., F.A.C.P., Brigadier General, (MC), U. S. Army, Professional Service Division, Office of the Surgeon General, Washington, D. C.

2. "The Management of Hyperthyroidism."

DAVID P. BARR, M.D., F.A.C.P., Professor of Medicine, Cornell University Medical College, New York, N. Y.

3. "Effort Syndrome and Allied Conditions in Civil and Military Practice."

JONATHAN C. MEAKINS, M.D., F.A.C.P., Brigadier, R.C.A.M.C., Director General of Medical Services of Canada, Ottawa, Ont.

INTERMISSION

Presiding Officer

ASA L. LINCOLN, M.D., F.A.C.P.

Governor for Eastern New York

4. "Medical Problems of the Middle East."

CRAWFORD F. SAMS, M.D. (by invitation), Colonel, (MC), U. S. Army, Medical Field Service School, Carlisle Barracks, Carlisle, Pa. (Recently returned from Cairo.)

5. "Medical Problems in an Army General Hospital."

MARSHALL N. FULTON, M.D., F.A.C.P., Lieutenant Colonel, (MC), U. S. Army, Chief of Medical Service, Valley Forge General Hospital, Phoenixville, Pa.

6. "Medicine with the Marines in Action."

DON S. KNOWLTON, M.D., F.A.C.S. (by invitation), Captain, (MC), U.S.N.R., Camp Surgeon, Camp Lejeune, New River, N. C. (Action in South Pacific with First Marine Division.)

PROBLEMS CONVIVIAL

6:30 p.m.—Cocktails

Washington Room, Mezzanine Floor,

Benjamin Franklin Hotel

7:15 p.m. Dinner—(Informal).

Ballroom, Benjamin Franklin Hotel

Toastmaster, GEORGE MORRIS PIERSOL

Official envoys of the Surgeons General of the United States were Brigadier General Hugh J. Morgan, U. S. Army, Captain Joseph A. Biello, District Medical Officer of the Fourth Naval District, U. S. Navy, Dr. R. C. Williams, Medical Director, District No. 1, U. S. Public Health Service.

Brief addresses were also made by Dr. Charles H. Cocke, First Vice President of the College, Asheville, N. C.; Brigadier Jonathan C. Meakins, Director General

of Medical Services of Canada, Ottawa; Commander Edward L. Bortz, (MC), U.S.N.R., A. C. P. Governor for Eastern Pennsylvania; Dr. O. H. Perry Pepper, F.A.C.P., President of the College of Physicians of Philadelphia, and Mr. E. R. Loveland, Executive Secretary of the College.

Among distinguished guests at the dinner meeting were members of the Board of Regents, Dr. William B. Breed, Boston, Chairman of the Board of Governors, Dr. Chauncey W. Dowden, Louisville, Vice-Chairman of the Board of Governors, Dr. Nelson G. Russell, Sr., Buffalo, Governor for Western New York, Dr. Alex. M. Burgess, Providence, Governor for Rhode Island, College Governors for the participating States, the Deans of all medical schools in Philadelphia, Dr. Hubley Owen, Director of Public Health of Philadelphia, Captain Jesse W. Allen, Commanding Officer of the U. S. Naval Hospital at Philadelphia, and Captain Clarence J. Brown, Executive Officer of the U. S. Naval Hospital of Philadelphia.

ELECTIONS TO FELLOWSHIP AND ASSOCIATESHIP

At a meeting of the Board of Regents of the American College of Physicians at Philadelphia, Pa., November 20, 1943, the following candidates were officially elected to the class of membership indicated:

ELECTED TO FELLOWSHIP

Adcock, John Delbert, Ann Arbor, Mich.
Ahronheim, J(acques) Heinz, Jackson, Mich. (AUS)
Allen, Lewis George, Kansas City, Kan.
Andujar, John Jose, Fort Worth, Tex.
Applebaum, Irving Loren, Newark, N. J. (AUS)
Ashby, John Edmund, Dallas, Tex.
Baganz, Crawford Norbert, Lyons, N. J. (USNR)
Ballmer, Robert Sidney, Midland, Mich.
Bell, Irving Russell, Edmonton, Alta., Can.
Bernstein, Arthur, Newark, N. J.
Bernstein, Benjamin Maurice, Brooklyn, N. Y.
Blalock, Joseph Rogers, Marion, Va.
Blankenhorn, Marion Arthur, Cincinnati, Ohio
Bloch, W(illiam) Austin, Louisville, Ky.
Blount, Rankin Clay, Lexington, Ky. (AUS)
Bohnengel, Charles Andrew, New York, N. Y. (AUS)
Bradford, William Hartsel, Dallas, Tex.
Brown, Omar Jesse, (MC), U. S. Navy
Byne, James Miller, Jr., Waynesboro, Ga.
Callomon, Verner Bickart, Pittsburgh, Pa.
Campbell, Eugene Paul, Philadelphia, Pa.
Carabelli, A(milcare) Albert, Trenton, N. J. (AUS)
Choate, Allyn Blythe, Charlotte, N. C.
Clark, H(arry) Dumont, Denver, Colo. (AUS)
Cleveland, Donald Ernest Howell, Vancouver, B. C., Can.
Cohen, Sumner S., Oak Terrace, Minn.
Conn, Jerome W., Ann Arbor, Mich.
Corlette, Marvin Brown, Pasadena, Calif. (AUS)
Crowell, Lester Avant, Jr., Lincolnton, N. C.
Davenport, Walter Paul, (MC), U. S. Army
DeArmond, (Albert) Murray, Indianapolis, Ind. (AUS)
Delarue, Edward Arthur, Jr., Richmond, Va. (AUS)

Delp, Mahlon Henry, Kansas City, Kan. (AUS)
Easom, Herman Franklin, Wilson, N. C.
Edwards, Joseph Castro, St. Louis, Mo. (AUS)
Eisner, Eugene A., New York, N. Y. (USNR)
Ershler, Irving, Binghamton, N. Y. (AUS)
Felson, Henry, Cincinnati, Ohio (AUS)
Ferris, Caryl Ray, Kansas City, Mo.
Friedenson, Meyer, New York, N. Y. (AUS)
*Gais, Elmer Stewart, New York, N. Y. (AUS)
Gammon, George Davis, Philadelphia, Pa.
Garvin, Curtis Ferbert, Cleveland, Ohio
Geeslin, Lawrence Easter, Atlanta, Ga. (AUS)
Goehl, Reinhold O., Grand Forks, N. D.
Grollman, Arthur, Winston-Salem, N. C.
Halley, Charles Robert Lee, Washington, D. C.
Halpin, Frank William, Fort Worth, Tex. (AUS)
Harper, Harry Taylor, Jr., Augusta, Ga.
Harrison, Meyer Max, Louisville, Ky. (AUS)
Harvill, T(homas) Haynes, Dallas, Tex. (USNR)
Haynes, Elmer, Madison, Wis.
Hernandez-Morales, Federico, San Juan, P. R.
Higgins, William Harrison, Richmond, Va.
Holbrook, Arthur Andrews, Milwaukee, Wis. (AUS)
. Jacobs, Sydney, New Orleans, La.
Jennes, Sidney Weinberg, Waterbury, Conn. (AUS)
Johnston, Elbridge Eugene, St. Johnsbury, Vt.
Jordan, William Riely, Richmond, Va.
Kelly, Frank Brazzil, Chicago, Ill.
Kilgore, F(ranklin) Hartman, Houston, Tex.
Kirk, Norman Thomas, (MC), U. S. Army
Kline, Edward Mahon, Cleveland Heights, Ohio
Knight, Alva Allan, Chicago, Ill.
Koppe, Harold Fredrick, Dayton, Ohio
Leedham, Charles Laurn, (MC), U. S. Army
LeFor, Frank George, Yakima, Wash.
Leopold, Henry Nathan, San Antonio, Tex.
Levy, Jerome Sickles, Little Rock, Ark. (AUS)
Levy, Robert Charles, Chicago, Ill. (AUS)
Lineberry, E(llis) Dice, Birmingham, Ala.
Lippschutz, Eugene John, Buffalo, N. Y. (USNR)
Loveman, Adolph Bernard, Louisville, Ky. (AUS)
Luchi, Angelo Luigi, Wilkes-Barre, Pa.
Lusk, Frank B., Chicago, Ill. (AUS)
MacBryde, Cyril Mitchell, Clayton, Mo.
MacNeal, Perry Scott, Philadelphia, Pa.
Macpherson, Walter Everett, Los Angeles, Calif.
Martin, John Walter, Jr., Cleveland, Ohio (USNR)
Martin, Louis Everett, Los Angeles, Calif.
Matthews, Edward de Saunhac, New Orleans, La. (AUS)
Matthews, Morgan Whitsitt, Shreveport, La.
Mignone, Joseph, New Haven, Conn. (USNR)
Minter, Merton Melrose, San Antonio, Tex.
Morgan, John Russell Egbert, Vancouver, B. C., Can. (RCAMC)

* Advancement to Fellowship as of April, 1944.

Morrison, Maurice, Brooklyn, N. Y.
Neff, Walter Scott, Virginia, Minn.
O'Brien, George Francis, Chicago, Ill. (AUS)
Ogaard, Adolph Thompson, New Orleans, La. (AUS)
Page, Irvine Heinly, Indianapolis, Ind.
Pendergrass, Eugene Percival, Philadelphia, Pa.
Penner, Abraham, New York, N. Y. (AUS)
Pernokis, Evans William, Chicago, Ill. (USNR)
Peters, Frank Hart, New York, N. Y.
Pleyte, Arthur A., Milwaukee, Wis.
Powers, Bruce Rankins, Knoxville, Tenn.
Quinlan, J(ames) William, Rochester, N. Y. (USNR)
Reich, Nathaniel Edwin, Brooklyn, N. Y.
Rothrock, Henry Abraham, Jr., Bethlehem, Pa. (USNR)
Schmitt, George Fredrick, Jr., Rochester, Minn. (USNR)
Schnitker, Maurice Arthur, Toledo, Ohio (AUS)
Segal, Harry L., Rochester, N. Y.
Shiflett, Emory Lee, Louisville, Ky.
Slagle, George Willard, Battle Creek, Mich. (USNR)
Smith, Frank Edward, Jr., New York, N. Y. (USNR)
Smith, Joseph Alphonsus, Metuchen, N. J.
Solomon, Walter Maximilian, Cleveland, Ohio (AUS)
Steele, Brandt Ferguson, Indianapolis, Ind. (AUS)
Steuer, Leonard Gerard, Cleveland, Ohio (AUS)
Stuppy, George William, Chicago, Ill. (AUS)
Swartz, Frederick Charles, Lansing, Mich. (AUS)
Teitelbaum, Myer, Detroit, Mich. (AUS)
Temple, R(ufus) Henry, Kinston, N. C. (AUS)
Thompson, J(oseph) Lawn, Jr., Washington, D. C. (AUS)
Tumen, Henry Joseph, Philadelphia, Pa.
Vaughn, Louis Dysart, Rochester, Minn. (AUS)
Vorzimer, Jefferson Jonas, New York, N. Y.
Waddill, J(ames) Franklin, Norfolk, Va. (AUS)
Walsh, John Joseph, Pottsville, Pa.
Wardrip, Buford Haven, San Jose, Calif.
Warren, Charles Ford, Brooklyn, N. Y.
Warren, Daniel Davis, Waco, Tex.
Way, Karl Duren, Akron, Ohio
Wiener, Alexander Solomon, Brooklyn, N. Y.
Wilfong, Clavel Tyrus, Roanoke, Va.
Wirtschafter, Zolton Tillson, Cleveland, Ohio (AUS)

ELECTED TO ASSOCIATESHIP

Adams, M. Vaun, Mobile, Ala.
Agerty, Horst Albert, Merion, Pa. (AUS)
Anderson, Forrest Nelson, Los Angeles, Calif. (AUS)
Archinard, John Joseph, New Orleans, La. (AUS)
August, Myron, Cleveland, Ohio
Babey, Andrew Michael, Brooklyn, N. Y.
Baker, Lynne Elmer, Jacksonville, Fla. (USNR)
Baker, Russel Lobach, Gaston, Ore. (AUS)
Ballinger, Joseph, New York, N. Y.
Barbato, Lewis, San Antonio, Tex. (AUS)

Beck, Luther Clagett, Honolulu, T. H.
Benenson, William Osler, Napanoch, N. Y. (AUS)
Benton, Louis Joseph, Ogdensburg, N. Y. (AUS)
Best, Gorden Newall, Council Bluffs, Iowa
Boland, Edward Ward, Los Angeles, Calif. (AUS)
Boylston, George Arthur, Wilmette, Ill. (AUS)
Bronstein, Lewis Herman, New York, N. Y. (AUS)
Burgert, Paul Haskell, Lake Forest, Ill.
Burney, Leroy Edgar, U. S. Public Health Service
Buttorff, Gordon Stephen, Louisville, Ky.
Caldwell, David Martin, Pittsburgh, Pa.
Caldwell, Hayes Woodrow, Rochester, Minn. (AUS)
Campbell, Joseph Lester, Ulster, Pa. (AUS)
Candel, Samuel, Brooklyn, N. Y. (USNR)
Cannon, Edward Aloysius, North Bergen, N. J.
Carnicelli, Thomas John, Framingham, Mass.
Carpenter, Gurth, Los Angeles, Calif.
Carroll, Howard Bertram, Chicago, Ill.
Chester, William Patrick, Detroit, Mich.
Christie, Harry C., New York, N. Y.
Coggeshall, Howard Cranor, Boston, Mass. (AUS)
Crago, Felix Hughes, Great Falls, Mont. (AUS)
Cramer, Charles, Jackson Heights, N. Y.
Crane, A(ugust) Reynolds, Brooklyn, N. Y.
Davidge, Lucious Lamar, Shreveport, La. (AUS)
Davis, John Preston, Winston-Salem, N. C. (AUS)
Del Duca, Vincent P., Camden, N. J. (AUS)
Dublin, William Brooks, Fort Steilacoom, Wash.
Duncan, Charles Newton, Dallas, Tex. (USNR)
Dunn, William LeRoy, Washington, D. C.
Dyer, John Lewis, New Orleans, La. (AUS)
Eichert, Herbert, Jacksonville, Fla. (USNR)
Ellis, Mackinnon, Bryn Mawr, Pa. (USNR)
Engle, David Edwin, Elmhurst, Ill. (AUS)
Epstein, Samuel, Brooklyn, N. Y.
Fahlstrom, Stanley, Chicago, Ill. (AUS)
Ferry, John Lumice, Akron, Ind. (AUS)
Foltz, Eliot Eugene, Chicago, Ill.
French, A(dam) James, Ann Arbor, Mich. (AUS)
Garry, Mark William, Milwaukee, Wis.
Gettelfinger, Wilfrid Charles, Louisville, Ky.
Gillespie, Delmar Robert, Rochester, Minn. (AUS)
Gilmour, Monroe Taylor, Charlotte, N. C.
Greenwood, Edward David, Topeka, Kan. (AUS)
Guthrie, Morris Baker, Columbus, Ohio (AUS)
Hackler, Robert Hardin, Jr., Washington, N. C.
Hall, William Earle Brandon, Port Huron, Mich.
Ham, George Caverno, Charlottesville, Va. (AUS)
Hamlin, Percy Gatling, Williamsburg, Va. (AUS)
Harrington, Peter Francis, Providence, R. I.
Hartwell, Alfred Stedman, Honolulu, T. H.
Heffner, Bain Lafayette, Boston, Mass. (AUS)
Hing, Ng William, Arecibo, P. R. (AUS)
Irvine, Jed Hotchkiss, New York, N. Y.

Jacobson, Samuel Maurice, Cumberland, Md.
Janjigian, Edward Rupen, Danville, Pa. (AUS)
Kennedy, J(ames) Allen, Nashville, Tenn. (AUS)
Keveney, John Joseph, Philadelphia, Pa. (AUS)
Kneedler, William Harding, Philadelphia, Pa.
Kubanek, Joseph Louis, Eloise, Mich.
Landau, Frederick Louis, Jr., Bronxville, N. Y. (AUS)
Laney, Richard Paul, Skowhegan, Maine (AUS)
Learn, G(eorge) Emerson, Mt. Morris, N. Y.
Lehnhoff, Henry John, Rochester, Minn. (AUS)
Liggett, Robert Samuel, Denver, Colo. (AUS)
Lloyd, Leo Walter, Denver, Colo. (AUS)
Lohr, Oliver Willison, Saginaw, Mich.
Madison, Frederick William, Milwaukee, Wis.
Manning, Isaac Hall, Jr., Durham, N. C. (AUS)
Martin, Thomas Wilson, Pittsburgh, Pa. (AUS)
McEvoy, Francis Joseph, Royal Oak, Mich. (USNR)
McKean, George Thomas, Detroit, Mich. (AUS)
Midelfort, Christian Frederik, Eau Claire, Wis.
Mitchell, Robert Hartwell, Plainview, Tex. (AUS)
Modell, Walter, New York, N. Y.
Monto, Raymond Walter, Detroit, Mich. (AUS)
Murphy, Paul, St. Louis, Mo.
Muse, Joseph Ennalls, Jr., Baltimore, Md. (AUS)
Nicholson, William McNeal, Durham, N. C.
Ochs, Louis, Jr., New Orleans, La. (AUS)
Patton, Paul Bellmonte, Philadelphia, Pa. (AUS)
Peasley, Elmus Day, Raleigh, N. C. (AUS)
Peters, Carey Moss, Boston, Mass. (AUS)
Peters, Gustavus Alfred, Rochester, Minn.
Peters, Michael, Telford, Pa. (AUS)
Peterson, Heyes, Wheeling, W. Va. (USNR)
Power, Paul Herschell, Waco, Tex.
Rattigan, John Patrick, Brighton, Mass.
Revell, Samuel Thompson Redgrave, Jr., Baltimore, Md. (AUS)
Ropes, Marian Wilkins, Boston, Mass.
Ross, Edward Still, Dallas, Tex. (USNR)
Rotkow, Maurice Julian, Des Moines, Iowa (AUS)
Ruskin, Arthur, Galveston, Tex.
Saphir, William, Chicago, Ill. (AUS)
Scherlis, Sidney, Baltimore, Md. (AUS)
Schuck, Carl Alfred, St. Louis, Mo. (AUS)
Schultz, Arthur Francis, Newport, Ky. (AUS)
Senekjie, Harry Archak, New Orleans, La.
Shenson, Ben, San Francisco, Calif.
Shpiner, Leonard Benjamin, Boston, Mass. (AUS)
Siver, Robert Hutton, Cockeysville, Md.
Sokolov, Raymond A., Detroit, Mich.
Solovay, Hyman U., Brooklyn, N. Y. (AUS)
Spellberg, Mitchell Abraham, Chicago, Ill. (AUS)
Stone, Charles Frederic, Jr., Atlanta, Ga. (AUS)
Sunday, Stuart Dos Passos, Baltimore, Md. (AUS)
Swinny, Boen, San Antonio, Tex. (AUS)
Swirsky, Morgan Yale, New Haven, Conn.

Tesler, James, Brooklyn, N. Y.
Thomas, Lawrence Jay, Washington, D. C.
Vander Meer, Ray(mond), Grand Rapids, Mich. (AUS)
Vinal, Raymond Gould, Norwell, Mass. (AUS)
Von Schulz, Augustine Paul, Baltimore, Md.
Warrick, George Wilks, Birmingham, Ala. (AUS)
Warshawsky, Harry, West Lebanon, N. H.
Weinberg, Samuel Joseph, Los Angeles, Calif. (AUS)
White, Asher Abbott, Minneapolis, Minn.
Wiesel, Bertram Hirsh, Tuscaloosa, Ala.
Willett, Forrest Munroe, San Francisco, Calif. (AUS)
Willis, Charles Alfred, Birmingham, Ala.
Wilner, Paul Robert, Washington, D. C. (AUS)
Wilson, Charles Pearson, Portland, Ore.
Wilson, Walter Howard, Greenville, N. C. (AUS)
Wollenweber, Henry L., Baltimore, Md.
Woods, Robert Max, Milwaukee, Wis. (AUS)
Wright, Robert Broy, Baltimore, Md.
Zimmerman, Bruce, Seattle, Wash.
Zindler, George Alexander, Battle Creek, Mich.

A. C. P. TO HAVE ELECTION OF OFFICERS, 1944

At a meeting of the Board of Regents of the College, November 20, 1943, at Philadelphia, it was voted unanimously to hold a limited Annual Session in the Spring of 1944 for the chief purpose of electing Officers, Regents and Governors and to conduct an Annual Business Meeting. The date of the meeting will be announced at least one month in advance; it is probable that the meeting will be held in Philadelphia at the time of the customary Spring Meeting of the Board of Regents and of the Board of Governors.

SPECIAL NOTICE

A course in Electrocardiographic Interpretation for *graduate physicians* will be given at Michael Reese Hospital by Dr. Louis N. Katz, Director of Cardiovascular Research. The class will meet each week, starting Thursday, February 17, for 12 weeks, from 7:00 to 9:00 p.m.

Further information and a copy of the program may be obtained on application to the Cardiovascular Department, Michael Reese Hospital, Chicago, Ill.

OBITUARIES

DR. WILLIAM OSLER ABBOTT

Dr. William Osler Abbott, of Philadelphia, died at Waquoit, Massachusetts, on September 10, 1943. He was a victim of myelogenous leukemia. The diagnosis was made in May of 1942, within a week after his arrival, as a Major with the 20th General Hospital, at Camp Claiborne, Louisiana, his first assignment in the Army. On account of his affliction he was honorably discharged from the military service on the following September 28, but already before that time had decided to devote the rest of his life to an investigative attack on the disease that he had acquired. On his return to civil life and apparently with scant thought for his personal welfare, he threw himself into his new research problem with the same industry, enthusiasm and earnestness that he had previously displayed in his gastrointestinal investigations. He died in the midst of his hematological work, but fortunately, since it was sponsored by, and was a part of a larger investigative effort being conducted by the Memorial Hospital group in New York City, under the direction of Dr. Cornelius P. Rhoads, significant results to which he made some contribution may yet be obtained.

Dr. Abbott's more important contributions to medical knowledge, however, were in the field of gastroenterology. Following his graduation in 1928 from the University of Pennsylvania Medical School, he had his internship in the University Hospital, then became associated with the Gastrointestinal Section of the Medical Clinic of that institution, and in 1941 was made an Assistant Professor of Medicine in his Alma Mater. For three years (1931–34) he was also connected, on a part-time basis, with the University's Department of Pharmacology, where he secured invaluable training under the direction of Dr. A. N. Richards. This experience in physiology intensified his interest in the type of investigative work then underway in the Gastrointestinal Clinic and undoubtedly aided in his significant contributions to the development and the use of an intubation method for studies of intestinal function, and later, in coöperation with Dr. Charles G. Johnston, to the application of the new technique to patients with obstruction of the bowel. While the latter was his most dramatic and clinically useful accomplishment, his original studies on various aspects of the physiology of the human digestive tract are doubtless equally important. In all he published about forty papers on medical topics, most of them on the subject of small intestinal intubation, but he also was the author of a characteristically whimsical article on "The Problem of the Professional Guinea Pig" and, just before his death, of one on "Trends in Cancer Research."

He was the son of the late Dr. Alexander C. Abbott, a professor of bacteriology and of public health and hygiene at the University of Pennsylvania. His mother was a niece of Sir William Osler, whom Dr. Abbott resembled physically and in many of his other traits, especially in his whim-

sicality, versatility, and capacity for work. In spite of this he never referred to his greatuncle, preferring recognition only on the basis of personal accomplishments.

He was a member of most of the important national societies to which an internist is eligible: in addition to his Fellowship in this College, he was a member of the Society for Clinical Investigation, the American Clinical and Climatological Association, the American Gastroenterological Association and the Association of American Physicians. He also was a Fellow of the College of Physicians of Philadelphia and a member of the Charaka Club of New York and of the Interurban Clinical Society. He was largely responsible for the success of a combined "Exhibit on the Small Intestine," which, in 1935, received a "Special Certificate of Honor" from the American Medical Association, the "First Award" of the Radiological Society of North America and the "Gold Medal" of the American Roentgen Ray Society.

Dr. Abbott's tastes were simple. He loved nature and was an accomplished fisherman and sailor. His athletic interests were limited to fencing in college, where he was the local champion. He spent his leisure time with his family, and as much of it as possible on Cape Cod. His special interest in the natural sciences is indicated by the fact that, on preparing to leave for the Army, he secured various standard textbooks on geology, stating that he knew less about that particular science than any other. Indeed, even before he fell ill in Louisiana, he had described in letters to friends certain observations on the geological phenomena of that locality.

In all of Dr. Abbott's personal relationships he was quiet, stimulating and coöperative. He thought straight and was original, practical and scientific in his approach to all new problems. Under stress, as well as in the ordinary walks of life, he was efficient, resourceful and ingenious; and always, as was amply demonstrated in his final illness, he was courageous. He was a leader and an inspiration to all who worked with him. He will be sorely missed, not only by his family, to whom he was unusually devoted, but by a wide circle of friends and acquaintances, including especially many of the active clinical investigators throughout the country.

T. GRIER MILLER, M.D., F.A.C.P.

DR. JULIAN MAST WOLFSOHN

Dr. Julian Mast Wolfsohn died at Stanford University Hospital in San Francisco, California, July 1, 1943, following an operation for acute intestinal obstruction.

Dr. Wolfsohn was born in San Francisco, California, in 1883. He obtained the degrees of A.B. in 1905, and M.S. in 1907, from the University of California. He graduated from the Johns Hopkins University School of Medicine in 1911. On return to California he joined the staff of the Leland

Stanford, Jr., Medical School at San Francisco in 1912. Over a period of years he advanced to Clinical Professor of Medicine. He was attached to the staffs of the San Francisco Hospital and the Hospital for Women and Children as Neuropsychiatrist; to the staff of the Mount Zion Hospital, San Francisco, as consulting Neurologist.

In 1917 Dr. Wolfsohn entered the service of the U. S. Army Medical Corps in World War I, and was for a time stationed in London, England. After two years he returned to civilian life in San Francisco, taking up again his work in Neurology and Neuropsychiatry. He became consulting Neuropsychiatrist to the Veterans' Administration Facility at Fort Miley and the Alcatraz Penitentiary, San Francisco.

Dr. Wolfsohn was a diplomate of the American Board of Psychiatry and Neurology; a member of the San Francisco Medical Society, California State Medical Society and the California Academy of Medicine. In 1921 he became a Fellow of the American College of Physicians. Other memberships were:—Fellow of the American Medical Association and member of the San Francisco Neurological Society.

During the past few years prior to his death, Dr. Wolfsohn was forced to limit his professional activities owing to chronic illness. He is survived by his widow and two sons.

<div align="right">

ERNEST H. FALCONER, M.D., F.A.C.P.,
Governor for Northern California

</div>

DR. ROBERT COPELAND MOONEY

Dr. Robert Copeland Mooney, Fellow of the American College of Physicians since 1931, died in Worcester, New York, on October 4, 1943, from cardiovascular disease after a five months' illness.

Dr. Mooney was born in Worcester, New York, on March 23, 1883. He was graduated from the Albany (New York) Medical College in 1908, following which he served an interneship in the Albany Memorial Hospital, continuing in postgraduate study at Harvard University and the Trudeau School of Tuberculosis. In 1910 he entered private practice at Speculator, New York, continuing there until 1916, when he moved to Gloversville, New York, and engaged in the general practice of medicine until 1918. He served as First Lieutenant, Medical Corps, United States Army, during World War I from 1918 to 1920. After his release from military service, he associated himself with the U. S. Public Health Service, later being transferred to the U. S. Veterans Bureau and Veterans Administration. From the beginning of his service in 1921 with the U. S. Public Health Service, he served at many stations, where his ability as a diagnostician was demonstrated. For several years prior to his death, he was a Senior Medical Consultant assigned to the Board of Veterans Appeals, Veterans Administration, Washington, D. C.

Dr. Mooney was a man of broad attainments and an ardent student, never tiring in his endeavor to keep in touch with modern medicine. His death is lamented by all who knew him.

<div align="right">CHARLES M. GRIFFITH, M.D., F.A.C.P.</div>

DR. WALTER RALPH STEINER

Dr. Walter R. Steiner died at the Hartford Hospital, Hartford, Connecticut, November 5, 1942. His health had been failing for several years, and in the spring of 1942 he developed an epidural abscess with generalized staphylococcic sepsis. The abscess was drained and the sepsis was controlled by penicillin, but a series of cerebral thrombi ensued which finally proved fatal after an illness of five months.

Dr. Steiner was born November 18, 1870, in Frederick County, Maryland, a descendant of Jacob Steiner, a German immigrant who settled in Maryland early in the 18th Century. Steiner's father, Lewis Steiner, also a physician, spent most of his professional life as a teacher of Chemistry and Pharmacy and his latter years, as a librarian. Walter Steiner inherited his father's scholarly tastes and love of books. His mother, Sarah Spencer Smyth, was a native of Guilford, Connecticut, where Dr. Steiner spent many summers in his youth.

Walter Steiner received his academic training at Yale, obtaining his A.B. in 1892. After two years of graduate work in Chemistry and Biology at Johns Hopkins University, he entered the second class of the newly-established Hopkins Medical School, receiving his M.D. in 1898. Then followed a two year appointment as house officer in the Johns Hopkins Hospital, where he served under Osler, Halsted and Kelly. At the close of this internship in 1900 he settled in Hartford.

Steiner's training and ability were early recognized in Hartford, and in 1901 he was appointed Pathologist and Bacteriologist to the Hartford Hospital. In 1905 he became also an Assistant Physician, and from 1908 to 1934 was an Attending Physician. As he became better known to the profession in Hartford and New Haven Counties, he received appointments as Consulting Physician to the Hartford Orphan Asylum, the Hartford Municipal Hospital, and the general hospitals in the neighboring cities of Meriden, Middletown, Manchester, New Britain, and Torrington.

Dr. Steiner was actively interested in both local and national medical societies. He took a lively interest in the affairs of the Hartford City, Hartford County, and Connecticut State Medical Societies. Of the last named he was Secretary from 1905 to 1912, Chairman of the Council from 1929 to 1933, and President in 1934–5. In all these capacities he exerted a pronounced influence on the policies of the Society. Dr. Steiner also represented Connecticut in the House of Delegates of the American Medical Association for many years and, in addition, was a member of the Associa-

tion of American Physicians, the Clinical and Climatological Association, the Medical Library Association, the American Association of the History of Medicine, and the Charaka and Beaumont Historical Clubs. He was for many years Secretary of the Congress of American Physicians and Surgeons.

Aside from his hospital and Medical Society activities, Walter Steiner's contributions to medicine were mainly along two lines: (1) his lifelong devotion to the library of the Hartford Medical Association, and (2) his contributions to medical literature.

As librarian to the Hartford Medical Society, he built up a collection of over 22,000 volumes, including complete files of the important medical journals. His labors were recognized by his colleagues who, during his lifetime, named the institution the Walter R. Steiner Library.

Dr. Steiner's most important writings were historical, and he was particularly interested in the early New England practitioners, both clerical and lay. He had a fund of information regarding these worthies and wrote, among others, of Elisha North, Elisha Perkins, Lemuel Hopkins, William Beaumont, and Nathan Strong. He published also several treatises for text books, and clinical articles on such varied subjects as venous thrombosis, dermatomyositis, hereditary hemorrhagic telangiectasia, focal and general infection, and diseases of the muscles.

In the death of Walter Steiner, the profession of the United States has lost an authority on some phases of medical history and of medical practice, and the people of Connecticut have lost an able, humane, and accomplished practitioner and a public servant of high ideals.

GEORGE BLUMER, M.D., F.A.C.P.

DR. WILLIAM HENRY LOHMAN

Dr. William Henry Lohman was born in West Orange, N. J., and died at his home in Brooklyn, N. Y., August 8, 1943. He received his medical degree at Columbia University College of Physicians and Surgeons in 1904 and spent the following year as resident pathologist and two years thereafter as intern at the Brooklyn Hospital. Most of Dr. Lohman's professional life was centered at the Brooklyn Hospital, where he rose to the rank of Chief Attending Physician in the year 1925, and continued to direct the Medical Division until his death. Earlier he spent a few years in the Outpatient Department of the Long Island College Hospital and taught Physical Diagnosis while he was there. In 1931 the Brooklyn Hospital became associated with the Long Island College of Medicine and Dr. Lohman was given the direction of the medical teaching with the rank of Professor of Clinical Medicine, a responsibility to which he gave much time and thought. In the meantime, he had given several years of service as Physician and Physician-in-Chief to the Brooklyn Thoracic Hospital. He was Consulting Physician to St. Johns Hospital and to the North Country Community Hospital in

Glen Cove, and for many years was a member of the Advisory Committee on Pneumonia Control, New York City Department of Health. During the First World War he served as Lieutenant in the U. S. Navy, serving as Chief of the Medical Service in Navy Base Hospital No. 1, Brest, France, and of the Camp Hospital No. 15, A.E.F. He was a member of the Kings County and New York State Medical Societies and was a Fellow of the American Medical Association, New York Academy of Medicine and the American College of Physicians (1937) and was a diplomate of the American Board of Internal Medicine.

Dr. Lohman was an accomplished internist, a wise and quiet gentleman, and a teacher whose influence will be felt for many years.

TASKER HOWARD, M.D., F.A.C.P.,
Brooklyn, N. Y.

DR. EDMUND PENDLETON SHELBY

Dr. Edmund Pendleton Shelby, F.A.C.P., Venice, Florida, died at Lexington, Kentucky, September 22, 1943, of carcinoma, at the age of 76.

Dr. Shelby was born November 26, 1866. He received his A.B. degree (1887) and his A.M. (1908), from the University of Kentucky. His medical training was received at New York University Medical College (1891). He interned at the Jersey City Hospital, 1891–92, and was later pathologist at the New York City Hospital. From 1897 to 1899, he was Director of the New York City Branch of the Loomis Sanatorium. From 1918 to 1934, he was Clinical Professor of Medicine at the University and Bellevue Hospital Medical College, New York City. He then removed to Venice, Florida, becoming Consultant in Medicine to the Florida Medical Center.

Dr. Shelby had been at one time President of the New York Pathological Society; also at one time Chairman of the Section on Medicine of the New York Academy of Medicine. He was a member of the Sarasota County Medical Society and Florida Medical Association. He was a Fellow of the American Medical Association, and had been a Fellow of the American College of Physicians since 1920.

ANNALS OF INTERNAL MEDICINE

SUBJECT INDEX

Volume 19, July–December, 1943